Intramural Activities Volume 3

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Division Of

Cancer Etiology

NATIONAL CANCER INSTITUTE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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ANNUAL REPORT

DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1988 through September 30, 1989

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ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

The Epidemiology and Biostatistics Program is the focus within 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 prevention of cancer. The Program employs epidemiologic approaches that are comprehensive and cover 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 combining epidemiologic and laboratory methods, and biostatistical and mathematical research on carcinogenic mechanisms and risk assessment.

Dr. Joseph F. Fraumeni, Jr. continues to direct the Program as the Associate Director for Epidemiology and Biostatistics. No major organizational changes occurred during the year, although the Program consolidated its move from the Landow Building in Bethesda, Maryland, to Executive Plaza North, located in Rockville, Maryland. The five 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). Formal site visits to the Radiation Epidemiology and Clinical Epidemiology Branches took place during this year, while appropriate actions were taken in response to site visits last year to the Biostatistics and Environmental Epidemiology Branches. The research and other activities of each Branch are described in the sections following this report, which focuses on the orientation, highlights, and direction of the overall Program.

INTRAMURAL RESEARCH

Continued emphasis was given this year to case-control and cohort studies evaluating key hypotheses in cancer etiology. Case-control studies of selected cancers were undertaken when high-risk communities were identified on the cancer mortality maps, major hypotheses were testable, or special resources became available. Laboratory methods were often incorporated into studies to help clarify exposures, preclinical responses, and mechanisms of carcinogenesis. Special emphasis was given to studies aimed at understanding the high rates of certain cancers in blacks and other minority groups.

Some descriptive surveys were also undertaken. Last year, an updated atlas was published to illustrate the geographic patterns of cancer mortality in the white population by state economic area in the 1970s. This year, a companion atlas for the nonwhite population is nearing completion. Preliminary findings

indicate the recent emergence of elevated mortality rates for prostate cancer along the South Atlantic coast, but for most other individual cancers there is a general trend toward geographic uniformity over time, as previously seen in the atlas for whites.

An examination of time trends was carried out for several cancers. For example, a study of age-specific patterns of lung cancer mortality found that rates peaked for both white and nonwhite males born around 1925-30 and females born around 1935-40, with declining rates among subsequent birth cohorts. These findings are consistent with cigarette smoking trends for these groups. A similar analysis of oral, esophageal, and laryngeal cancers revealed peak mortality among females born around 1915-25, which was not as apparent among males, suggesting a role for poorly understood risk factors, perhaps nutritional, combined with the well-documented effects of alcohol and tobacco consumption, which have driven the trends for these cancers in males.

Biochemical epidemiology: Multidisciplinary collaborative investigations, which integrate epidemiologic and experimental approaches, are being emphasized to clarify cancer risk factors at the biochemical and molecular level. These investigations involve the collection of biological specimens as a component of epidemiologic studies. Laboratory analyses of the specimens provide insights into factors that increase or inhibit cancer risk, as well as information on preneoplastic events, host susceptibility, and mechanisms of carcinogenesis.

For many cancers, laboratory components of epidemiologic studies can add substantially to our knowledge of risk factors. For example, the role of diet and nutrition on cancer risk is being assessed by measuring biological levels of micronutrients (e.g., vitamins A and C), trace metals (e.g., selenium), and fats. Host determinants for certain forms of cancer are being assessed in studies that measure levels of endogenous hormones, immunological characteristics, and genetic traits that may predispose to cancer. The role of infectious agents is being investigated in studies to detect human retroviruses and papillomaviruses that are associated with the risk of certain types of cancer. Exposure to potentially carcinogenic chemicals are being evaluated by measuring their ability to combine with cellular nucleic acids or proteins through adduct formation. Interactions with laboratory scientists and innovative strategies of biochemical epidemiology are strongly encouraged as a means of better understanding the origins of cancer and the means of its prevention.

Tobacco and alcohol: Several investigations helped clarify the role of tobacco and alcohol in cancer risk. In the largest investigation of oral and pharyngeal cancer yet conducted (1200 cases and 1300 controls), smoking and drinking were shown to be the dominant risk factors. The large study size enabled the first clear demonstration of effects of alcohol consumption among lifelong nonsmokers, and indicated that smoking and drinking tend to combine more in a multiplicative than additive fashion to cause oral cancer. Among heavy smokers and drinkers, the risks of oral/pharyngeal cancer rose over 35-fold. Also, risks were shown to fall sharply following cessation of smoking, suggesting that smoking affects primarily a late stage in oral carcinogenesis.

Smokeless tobacco was implicated as a risk factor among nonsmokers, consistent with earlier NCI reports of a similar association with oral cancer. However, the number of users in this study was too small for detailed analysis of the

relative influence of snuff vs. chewing tobacco. Smokeless tobacco also appeared as a risk factor in a case-control study of soft-tissue sarcomas, especially for tumors arising from the upper gastrointestinal tract, the lung and pleura, and the head, neck, and face region. This new finding is noteworthy, given the increasing use of smokeless tobacco among young people.

Tobacco and alcohol were found to be the main determinants of esophageal cancer in coastal South Carolina, where mortality rates for this tumor have long been elevated among blacks. Consumption of local moonshine whiskeys, reported by nearly 90% of the black male patients, appeared at least partly responsible for the high rates in this area. Laboratory analyses of the moonshine whiskeys for possible carcinogenic ingredients are underway.

In a cohort study of mortality among 250,000 U.S. veterans administered a questionnaire in the 1950s, mortality from leukemia, particularly of the myeloid type, was shown to be increased among smokers, confirming reports from other studies that leukemia is a smoking-related cancer.

In a case-control study of invasive cervical cancer in four Latin American countries, where rates of this cancer are high, the effect of cigarette smoking on cervical cancer risk was primarily among women infected with human papillomaviruses types 16 and 18.

Occupation: Most chemicals known to be carcinogenic in humans were first identified in studies of occupational groups, whose exposures are often heavier and of longer duration than those typically encountered by the general population. Occupational studies continue to provide opportunities to identify and clarify environmental causes of cancer. Case-control and cohort studies are underway to investigate a wide range of exposures, including acrylonitrile, formaldehyde, pesticides, organic and inorganic dusts, metal fumes, and organic solvents (e.g., trichloroethylene, perchloroethylene, methylene chloride, benzene, benzidine). A number of methodologic projects have been designed to improve exposure assessment, evaluate delivered dose, and modify existing data resources for occupational studies.

Several investigations are underway among workers having contact with pesticides. In a case-control study, soft-tissue sarcomas were excessive among Kansas farmers reporting use of animal insecticides. Risks rose to nearly 5-fold among those first exposed in the 1940s, and appeared to be more strongly linked to organochlorine insecticides than other chemicals. In studies of U.S. Department of Agriculture employees, leukemia was elevated among agricultural extension agents, and non-Hodgkin's lymphoma among soil and forest conservationists. For both tumors, the risks rose with number of years employed. Analyses are underway of data from case-control studies of lymphatic and hematopoietic cancer in Nebraska, Iowa, and Minnesota to further assess risks from pesticide exposures among farmers. Also, cohort mortality studies involving workers at a national lawn care company and at county noxious weed departments are in progress to evaluate risks from herbicide exposures.

Several investigations have noted an intriguing inverse relationship between physical activity associated with the job and the risk of colon cancer. To evaluate this observation, a case-control study using data from the Missouri Tumor Registry found that persons holding jobs requiring high physical activity had a 30% reduced risk of colon cancer than workers holding low-activity jobs.

The deficit was most pronounced for cancers of the descending colon and cecum. Similar results were obtained in a study using follow-up data from the First National Health and Nutrition Examination Study (NHANES), where the relative risk for colorectal cancer among men in high-activity jobs was 0.6 that of men in low-activity jobs. Lung cancer among men and breast cancer among women also showed inverse associations with job-related physical activity in the NHANES study. These relationships could not be explained by the effects of smoking, body mass, socioeconomic status or diet. Leisure-time physical activity, however, was not associated with the risk of any cancer. A cohort mortality study of 300,000 U.S. veterans is further evaluating associations between job-related physical activity and mortality from cancer and other causes of death.

Although smoking is the predominant cause of lung cancer, its occurrence may also be associated with occupational exposures. One study found that Chinese hematite miners exposed to radon and silica had an excessive risk of lung cancer. In the U.S., elevated risks were described among chromium pigment workers. A study in Missouri found that occupational risks varied by histologic type. Adenocarcinoma of the lung was elevated among persons employed as furniture workers, plumbers, printers, and electricians, while squamous-cell cancer was elevated among fire fighters, brick masons, and roofers.

A mortality study of over 36,000 members of the United Furniture Workers of America uncovered elevated risks for leukemia and non-Hodgkin's lymphoma among workers in the wood furniture industry, and slight excesses for cancers of the lung, stomach, and colorectum among those in the metal furniture industry. Mortality from nasal cancer was not excessive, but only two deaths were expected. An extended follow-up of this cohort is in progress to clarify the associations found to date.

U.S. Coast Guard marine inspectors, who come into contact with a variety of chemicals during inspection of ships and barges, experienced elevated mortality from cirrhosis of the liver, motor vehicle accidents, liver cancer, and leukemia. Mortality from these diseases rose with increasing cumulative exposure to chemicals.

Detailed analyses of occupational data collected during the National Bladder Cancer Study indicated that the proportion of bladder cancer attributable to occupation was about 20% in men and 5% in women. The relative risks were generally similar in men and women, although the frequency of exposure to occupational carcinogens was substantially lower in women. While the contribution of high-risk occupations to bladder cancer among nonwhite men was similar to that among white men, there appeared to be racial differences in their specific exposures, even among workers in the same industry or job title category.

Under an NCI/NIOSH Interagency Agreement, a case-control study of lung cancer in the Teamsters Union revealed that long-term truck drivers, who were potentially exposed to diesel exhaust, have about a 50-90% increased risk, after control for smoking. The actual level of diesel exposure among truck drivers is unknown, and industrial hygiene studies in the trucking industry are underway to clarify the extent of this exposure.

Detailed assessment of exposures is a major component of occupational studies. Methodologic investigations in industrial hygiene are evaluating current assessment procedures and attempting to improve their capabilities. A new semi-quantitative assessment procedure, designed for case-control studies, reduced the number of estimates required by 85%, but retained a high level of agreement (89%) with the traditional and more time-intensive method. Ongoing efforts are designed to compare different approaches in developing quantitative exposure estimates in cohort studies, to incorporate biochemical monitoring results into historical assessments, and to assess the intra- and inter-individual reliability of estimates provided by industrial hygienists.

Radiation: The relationship between cancer risk and ionizing radiation is being studied to improve estimates of risk associated with low doses and to provide insights into basic mechanisms of carcinogenesis. Better data on low-level effects are needed to base regulatory and other decisions about the potential hazard from medical, occupational and environmental exposures, and to assess the value of exposure avoidance as a means of cancer prevention.

A new survey of breast cancer among women treated for scoliosis revealed elevated risks following an average of 40 x-rays to the spine to monitor curvature. Most of the exposures occurred during childhood or adolescence, suggesting that the developing breast is especially susceptible to the carcinogenic effects of radiation. A case-control study of breast cancer among atomic bomb survivors found that risk appeared greater among women who became pregnant after exposure. Among cervical cancer patients treated with radiation, no overall risk of breast cancer was detected following doses on the order of 0.30 gray. However, there was a suggestion of a dose response among women whose ovaries had been surgically removed.

A study of adult leukemia and lymphoma, utilizing prepaid health plans, indicated that diagnostic x-rays may not be causally related to these diseases, but simply associated with conditions that portend their development. For multiple myeloma, however, there was a suggestion of increasing risk with increasing number of x-rays. Low doses of diagnostic iodine-131 were not found to increase the risk of thyroid or other cancers in over 35,000 patients in Sweden, indicating that the carcinogenic potential of this exposure is much less than that of x-rays or gamma rays. For the first time, excess risks of breast and liver cancers were suggested among German patients treated with radium-224. A large excess of osteosarcoma was also observed, but no increase in leukemia. Liver cancer and leukemia were also found to be elevated following exposure to thorotrast among Danish epileptic patients.

Low-dose radiotherapy to treat uterine bleeding induced many more leukemias than higher-dose radiotherapy to treat cancers of the cervix and breast, suggesting the importance of cell-killing in defining dose-response relationships. Adrenal damage by radiation to treat cervical cancer may have contributed to the low breast cancer risk seen even among postmenopausal women, especially in view of the low levels of estrogens and androgens that were also detected in this exposed group. Dose-response relationships after radiotherapy for cervical cancer were reported for 16 cancer sites, including the stomach, uterus, rectum, bladder, vagina, kidney and ovary.

The long-term follow-up of patients who received multiple chest fluoroscopies during lung collapse therapy for tuberculosis has continued. Several new surveys confirm that repeated, relatively low radiation doses impart some increased risk of breast cancer and that risk is related to dose in a linear manner. The risk appears cumulative, with those exposed during adolescence being especially vulnerable, while women over 40 years of age at exposure are at little or no excess risk. No excess risk of lung cancer was found, despite average cumulative doses on the order of 1 gray, and no increase was seen for leukemia. In the Boston area, clinical examination of persons irradiated as children for enlarged tonsils identified an excess of thyroid nodules following doses on the order 0.24 gray. However, the risk was much lower than that estimated from a mail survey, suggesting that questionnaire studies might be misleading due to underascertainment of thyroid disease among non-exposed populations. In southern China, women residing in areas of high natural background radiation due to radioactive monazite sands were not found to have a higher prevalence of thyroid nodular disease than women in neighboring areas. The absence of any differences, based upon clinical examination, suggests that protracted exposures to very low levels of ionizing radiation throughout life are not associated with thyroid disease. Medical x-ray workers in China, however, were found to have a 50% higher risk of developing cancer than other specialists, with notable excesses of leukemia, breast and thyroid cancers.

Radiation treatments for ringworm of the scalp in Israel were found to increase the risk of thyroid cancer and nodular disease following doses on the order of 0.09 gray. This study is one of the few human epidemiologic surveys detecting an increase in cancer at such a low dose. For the first time, a dose-response relationship was found for cancers of the brain and central nervous system. Skin cancer was also increased significantly above expectation. Leukemia was not linked to radiotherapy for breast cancer, providing further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue. Women irradiated for Hodgkin's disease at a young age were found to be at high risk for breast cancer. Radiotherapy for Hodgkin's disease also appeared to explain the subsequent excess risk of leukemia and cancers of the lung, stomach, bone and soft tissue. The risk of second cancers of the thyroid was strongly associated with radiation therapy in an international study of over 9,000 children with cancer.

Special emphasis is being placed on clarifying the role of indoor radon exposure, which may contribute to as much as 10% of all lung cancers in the U.S. based on risk models utilizing data from earlier NCI studies of uranium miners. More reliable data should come from ongoing case-control studies of lung cancer that involve careful measurements of indoor radon. A new survey was initiated to evaluate cancer mortality among populations residing near nuclear reactor facilities.

Ultraviolet (UV) radiation has been investigated as an important cause of melanoma and non-melanoma skin cancer. For melanoma, childhood and intermittent (recreational) exposures are especially important, while for other skin cancers, cumulative (occupational) exposures play a key role. Also clarified were predisposing host factors in the form of skin complexion for all types of skin cancer, and dysplastic nevi for melanoma. Since sunlight is the major source of UV radiation, there has been concern about the depletion of stratospheric ozone, especially in view of recent reports of "ozone holes" over Antarctica and decreasing trends in stratospheric ozone levels (mostly during

winter months in the northern hemisphere). However, surface measurements of solar UV radiation have shown no increasing trend as yet, but further monitoring of UV exposures and skin cancer incidence is warranted in collaboration with other Federal agencies. Studies are also underway to clarify the possible role of electromagnetic radiation in certain cancers, especially childhood leukemia.

Environmental pollution: Research to evaluate risks of cancer in relation to exposure to general environmental pollution continued during the year, using environmental measurements whenever possible. In a collaborative study in Shanghai, China, risk of lung cancer was increased among women reporting greater frequencies of high temperature wok cooking, increased house smokiness and eye irritation when cooking, and greater use of rapeseed cooking oils. This finding is intriguing since Chinese scientists have reported that rapeseed volatiles are mutagenic in the Ames test. In Shenyang, China, the risk of lung cancer rose with greater exposure to indoor pollution from coal-burning Kang and other home-heating devices that generate high levels of polycyclic hydrocarbons. Industrial sources of pollution were also implicated in this study, with a 3-fold increased risk of lung cancer among males living within one kilometer of a large copper smelter that emits inorganic arsenic and other metallic pollutants. Radon is also being evaluated in Shenyang, with alpha-track dosimeters placed in the homes of female lung cancer cases and controls. Similar studies to evaluate the impact of indoor radon levels are underway in collaboration with investigators in New Jersey, Missouri, and Sweden.

An increased bladder cancer risk was found to be associated with the level of intake of chlorinated tap water, with long-term consumers having the greatest risk. To clarify these findings, a new case-control study was initiated to investigate cancer at six anatomical sites, including the bladder. Data from the first phase of this study are now being analyzed, particularly with regard to the influence of agricultural chemicals and chlorination by-products as cancer risk factors.

Nutrition: Evidence from international correlations and migrant populations suggests that diet and nutrition are important in cancer etiology, but specific dietary risk factors have not been well established in case-control and cohort studies. The Program continues to test and generate hypotheses on the role of diet and nutrition on cancer risk.

Using the follow-up of the First NHANES cohort, studies were conducted in collaboration with the Division of Cancer Prevention and Control (DCPC) to evaluate the effects of serum cholesterol, serum vitamin A, and height and weight on cancer risk. Low cholesterol was a risk factor for both cancer incidence and mortality, especially among males. The inverse cholesterol-cancer relationship in men was present for determinations made 6 or more years before diagnosis of cancer, suggesting that lowered serum cholesterol may not simply result from preclinical disease. Further analysis revealed inverse associations with a number of cancer sites related to smoking, including the lung, bladder, pancreas, and cervix, with the relationships persisting even after adjustment for smoking.

Vitamin A levels at baseline examinations were significantly lower in prostate cancer cases than controls. Individuals in the lowest quartile of vitamin A had a relative risk of 2.4 compared to those in the highest quartile. Since

risk estimates did not decrease with increasing time until diagnosis, metabolic effects of early disease are not a likely explanation of these results.

Results from a case-control study of fecal mutagens and colorectal cancer showed a decrease in fecapentaene excretion among the cases, compared to controls, that could not be explained by the effects of diagnostic work-up or surgery. Most mutagenic activity could be explained by fecapentaene content. However, non-fecapentaene Salmonella TA-98 mutagens were significantly elevated in cases compared to controls. Possible dietary origins of this mutagenicity, including cooked meats, are being investigated.

In the Breast Cancer Detection Demonstration Project (BCDDP), an upward trend in breast cancer risk was associated with height. Relative weight was a risk factor among women over 50 years of age, but among younger women an inverse association was observed. The latter effect was restricted to small tumors and probably reflects a detection bias. A relationship to height was also found in data from the NHANES, suggesting a role for early diet in the etiology of breast cancer. A study is nearing completion among American women of Asian ancestry to assess what aspects of the Western diet or lifestyle are associated with the rising breast cancer risk in successive generations of migrants, and to evaluate whether dietary factors are especially important during childhood and adolescence. A multicenter case-control study of endometrial cancer is underway to assess dietary factors and the role of obesity, as measured by dietary recall, anthropometry, and biochemical measurements.

In a large community-based case-control study of cervical cancer in the U.S., women in the highest quartiles of intake of carotenoids, vitamin A, vitamin C, and folacin had adjusted relative risks of invasive squamous-cell cervical cancer comparable to women in the lowest quartiles, although their micronutrient intake was estimated to be 3-4 times as high. Risk was not affected by intake of various food groups, including fruits and vegetables. These generally negative findings stand in contrast to previous epidemiologic studies that suggested a protective role for micronutrients.

Methodologic research to buttress ongoing etiologic studies of nutrition and cancer is being carried out in cooperation with the National Institute of Standards and Technology (NIST). Both prospective and retrospective studies have consistently demonstrated that vegetables and fruits reduce the risk of lung cancer and possibly other cancers. Beta-carotene seems a likely protective factor, but other carotenoids have not been adequately explored. Thus, methods are being developed to recover and measure the major carotenoids in stored serum to permit evaluation of their potential cancer-inhibitory effects in prospective studies.

Vitamin C has been proposed to reduce the risk of certain cancers, notably of the stomach. Measurement of vitamin C is difficult, however, because of its lability in collected sera samples. In cooperation with NIST, a method is being developed that will measure the vitamin in its unoxidized state, such that the analysis will reflect actual biological levels.

In a multicenter study in four geographic areas of the U.S., fruit consumption was shown to be protective for oral cancer, with risks among those in the highest quartile being only half those in the lowest. The association held for

fruits both high and low in vitamin C, suggesting that other nutritive or non-nutritive components may be involved. Low fruit intake was also shown to increase the risk of esophageal cancer in the high-risk area along coastal South Carolina.

Nutritional hypotheses were examined in several collaborative international studies. In a case-control study in Shandong, China, stomach cancer patients tended to consume more salted foods and sour pancakes, and less fresh vegetables. The protective effects were most prominent for vegetables of the allium class, including garlic, which is interesting in view of the tumor-inhibitory properties of allium reported from experimental studies. Laboratory analyses of the sour pancakes and allium vegetables are underway. In a multicenter study of stomach cancer in high- and low-risk areas of Italy, garlic was also shown to be protective, as was consumption of fresh (but not cooked or preserved) fruits and vegetables.

In Linxian, China, consumption during adulthood of pickled vegetables was not found to be the strong risk factor as previously suspected. Instead, the cases were characterized by lower fluid and higher wheat and corn intake, similar to Iran where exceptionally high esophageal cancer rates have also been found. Large-scale randomized nutrition intervention trials continued in Linxian. Two studies, now in their fourth and third years, 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. The results may have important implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

Medications: Studies were continued to evaluate the carcinogenic effects of hormones, cytotoxic drugs, and other compounds. In a collaborative case-control study of 23,000 Swedish women who used menopausal hormones, an excess risk of endometrial cancer (showing a dose-response with both duration of use and strength of medication) was noted for estrogens unopposed by progestational agents. For women who used only the combination regimen (i.e., estrogen plus progestogen), no excess risk of endometrial cancer was detected. However, for those women who switched from unopposed to opposed regimens, some excess risk persisted. Evaluation of breast cancer risk revealed a 60% increase in breast cancer after 10 or more years of replacement estrogen therapy. This excess was not diminished by the addition of progestogen to the regimen, and in fact, the risks were somewhat higher and seen with shorter durations of use.

Case-control studies of cervical cancer in the U. S. revealed an increased risk associated with oral contraceptives, especially with long-term use, after adjusting for screening history and other risk factors. In high-risk areas of Latin America, however, oral contraceptives appeared to have little effect on squamous-cell tumors, but its use was associated with about a doubling of risk of adenocarcinomas. In a collaborative study in Australia, the risk of *in situ* cervical cancer was strongly influenced by extended usage of oral contraceptives. A case-control study of complete hydatidiform mole in China revealed a significant trend in risk with years of oral contraceptive usage. In view of several reports suggesting that early and extended use of oral contraceptives may increase the risk of breast cancer, a large-scale population-based case-control study is in the planning stages.

An increased risk of leukemia and preleukemia was associated with alkylating agent therapy used for breast cancer, whereas no excess risk was apparent following radiotherapy. In studying the late effects of treatment for childhood cancer, actinomycin-D appeared to enhance the risk of thyroid cancer following radiotherapy, but alkylating agents were not associated with risk of this cancer. In contrast to experimental and clinical observations, phenobarbital and hydantoin were not clearly linked to increased cancer risks among epileptics heavily exposed to anti-convulsant drugs in Denmark. An association, suggested in an earlier NCI study, between renal pelvis cancer and acetaminophen-containing analgesics is being evaluated in a multicenter case-control study of this tumor.

Genetic susceptibility: Based on epidemiologic and clinical observations by NCI investigators, and collaborations with laboratory scientists, family cancer syndromes have provided several clues to mechanisms of host susceptibility. Recent developments include localization of the gene for the more common form of neurofibromatosis (NF-1) to the long arm of chromosome 17, near the gene for the receptor of the nerve growth factor; and the less common form (NF-2, acoustic neuromas) to the long arm of chromosome 22. In progress is a multifaceted clinical study of both forms of NF in collaboration with other NIH investigators. The results show that the gene action produces far greater impairment within the nervous system than was known previously. Imaging of the brain by nuclear magnetic resonance provides early detection of acoustic neuromas in NF-2, which permits prompt removal and protects against drowning due to the loss of the sense of balance.

Multidisciplinary studies are delving further into the molecular biology of several heritable cancer syndromes identified by NCI staff. A prospective study of 24 kindreds is near completion on the occurrence of new neoplasms, after initial ascertainment of the dominantly inherited Li-Fraumeni cancer family syndrome, featuring sarcomas, breast cancer, and certain other tumors. Preliminary analyses indicate that survivors of the first cancer have a 30% frequency of second neoplasms, including several radiogenic tumors. In laboratory studies of the syndrome, tissue specimens from several large families are being collected for linkage analysis using the polymerase chain reaction to amplify genetic sequences from family members who have died of cancer. In addition, long-range pulse field gel electrophoresis is being used to localize the X;18 translocation breakpoints that characterize synovial sarcoma. In a remarkable family with 3;8 translocation and predisposition to renal adenocarcinoma, new foci of renal carcinoma have recurred in two family members whose initial kidney tumors had been resected 12 years ago. Fresh tissue specimens have been collected for cytogenetic and molecular studies to permit analyses of additional changes leading to renal cancer development in individuals with a constitutional derangement of chromosome 3p. In a Wilms' tumor family with seven affected cousins, arrangements have been finalized to establish transformed lymphocyte lines from 60 members of the kindred for linkage analysis. In addition, paraffin blocks from patients with the aniridia-Wilms' association have been obtained and oligonucleotide primers prepared to seek additional changes in chromosome 11p in patients with an inborn 11p13 deletion.

NCI epidemiologists reported a decade ago that dysplastic nevi were precursor lesions for melanoma in members of melanoma-prone families. Approximately 10% of all melanomas occur in individuals with a family history of melanoma. In

these families, melanoma and dysplastic nevi represent an autosomal dominant single-gene trait. In collaboration with laboratory investigators, the gene has just been located on chromosome 1p36. In addition, about half of all melanomas arise in the 5-8% of the general population who have dysplastic nevi, with individuals in this group having about a sevenfold increased risk of developing cutaneous melanoma. It has recently been found that about 80% of unselected individuals with dysplastic nevi have at least one other affected family member. This finding suggests that physicians should examine all available family members for the presence of nevi and melanoma, and institute periodic medical surveillance and preventive measures to reduce sunlight exposure and sunburns.

Melanoma-prone families will continue to be investigated in epidemiologic and genetic studies. Attempts will be made to confirm the localization of the melanoma susceptibility gene on chromosome 1p36 in additional high-risk families and to develop new DNA probes closer to the actual gene site. These efforts are directed toward the goal of isolating and characterizing the gene's function and product so as to elucidate the mechanism of melanoma susceptibility. Once the gene is isolated, subjects from a new case-control study of melanoma will be evaluated for the presence of the gene. Since the incidence of cutaneous melanoma is rapidly increasing in the population, these investigations may provide new insights into preventive measures.

Studies in the area of pharmacogenetics have revealed a relationship between lung cancer susceptibility and the extent to which the antihypertensive drug debrisoquine is metabolized. Differences in the ability to metabolize debrisoquine have been found between blacks and whites, and a new case-control study of lung cancer has been initiated to follow-up on these findings. Another pharmacogenetic study is investigating the relationship between bladder cancer susceptibility and the heritable metabolic capacity for acetylation.

Infectious agents: Advances in laboratory techniques, such as viral isolation and molecular detection approaches, have opened new avenues for exploring the role of viruses in cancer etiology. The risk of cervical cancer was once thought to be related to infection by herpesvirus type 2, but more recent attention has focused on the role of human papillomaviruses (HPV). Epidemiologic studies are employing DNA hybridization techniques to assess the association between type-specific HPV infection and cervical cancer risk. In a case-control study of invasive cervical cancer in Latin America, detection of HPV types 16 or 18 in cervical cells (as measured by DNA filter *in situ* hybridization) was associated with a fivefold excess risk. In a case-control study of cervical dysplasia in Washington, D.C., a fourfold excess risk associated with detection of any HPV type was observed. Blacks were more likely than whites to have HPV detected, consistent with the higher incidence rates for cervical cancer and dysplasia among blacks. In another study of dysplasia in Washington, D.C., a tenfold risk was associated with detection of any HPV type. The elevated risk estimates persisted in all three studies after statistical adjustment for other known risk factors.

Methodological studies revealed that some caution must be exercised in interpreting results of HPV-DNA hybridization assays, particularly since there was considerable variation in typing even when the "gold standard" Southern

blot assay was utilized. To address the natural history of HPV infection, a prospective study of early infection in approximately 25,000 cytologically normal women has been initiated. Follow-up is scheduled to last three years.

The discovery in 1980 of the first human retrovirus, human T-cell lymphotropic virus type I (HTLV-I), has resulted in new insights concerning cancer causation. It also led to the recognition that HTLV-I is associated with other chronic diseases, particularly of the nervous system. Two forms of leukemia have thus far been identified: adult T-cell leukemia (ATL), involving a direct mechanism; and chronic lymphocytic leukemia of B-cells, through indirect mechanisms. A chronic demyelinating neurologic syndrome, called tropical spastic paraparesis (sharing some features with multiple sclerosis), is also associated with HTLV-I. Starting in 1982, a series of long-range epidemiologic studies has been undertaken by Program staff in several HTLV-I viral-endemic areas.

Several important observations have emerged recently by coupling HTLV-I exposure data from a large Jamaican population survey to a population-based registry of ATL. The risk for ATL in seropositive cases was found to be elevated 35-fold compared to controls. Also, modeling ATL incidence with HTLV-I prevalence suggested that risk for ATL is especially high in individuals exposed early in life to the virus, with a 3-5% lifetime risk for leukemia.

Studies of special populations have identified that about 20% of infants of HTLV-I seropositive mothers become infected, primarily due to breast feeding. Sexual transmission of HTLV-I has been evaluated in several populations, confirming prior observations that male-to-female transmission predominates, accounting for the disproportionate excess of female positives in older age groups. Female-to-male transmission may involve cofactors, such as the presence of other sexually transmitted diseases and ulcerative genital lesions. Parenteral transmission via transfusion and through sharing of needles is also linked to spread of HTLV-I. These studies have played a significant role in helping to formulate this country's public health policies for screening the U.S. blood supply for HTLV-I. Finally, recent data suggest that coinfection with human immunodeficiency virus (HIV) and HTLV-I may accelerate progression to AIDS when compared with individuals infected with HIV alone.

HIV, the etiologic agent of acquired immunodeficiency syndrome (AIDS), is associated with a significant cancer excess, as quantified through surveys using population-based registries in areas with a high incidence of AIDS. Most prominent among HIV-infected persons are Kaposi's sarcoma and non-Hodgkin's lymphoma, with suggestive excesses of hepatocellular carcinoma. Several cohorts are under surveillance to clarify the natural history of AIDS, the risks of cancer, and the mechanisms for cancer susceptibility. As patients are successfully treated with drugs, such as AZT, and experience longer-term survival, further increases in cancer risk may be anticipated as lethal opportunistic infections are averted. Kaposi's sarcoma is a current focus of research in the U.S. and overseas, employing newly developed growth factor approaches.

Studies are ongoing to clarify the role of hepatitis-B infection in liver cancer, utilizing material from the unprecedented 1942 epidemic of post-vaccinal hepatitis in the U.S. Army. The first phase of the study showed that the epidemic was caused by the B virus and that hepatitis-B markers persisted

for at least 43 years after infection. In the second phase, a cohort mortality study of 60,000 veterans, the small excess of primary hepatocellular cancer found in the 1946-1983 period was far less than expected from current estimates of the likelihood of transition from the carrier state to cancer. The third phase, a case-control study based on discharges from hospitals of the Veterans Administration, is nearing completion.

In view of the association between hepatitis-B infection and liver cancer in from Asia and Africa, a pilot study of approximately 2,000 Army veterans, compensated in 1957 for residuals of wartime hepatitis infections, is being undertaken. The objective of the study is to investigate the pathogenesis of liver cancer, especially in individuals whose hepatitis infections arose from the B virus. Under consideration is a further study of hepatitis-B carriers among Red Cross blood donors, especially since a preliminary evaluation revealed some excess mortality from liver cancer among carriers.

An investigation is being planned to study liver cancer among A-bomb survivors in Hiroshima and Nagasaki, with a focus on both ionizing radiation and hepatitis-B infection. Hiroshima and Nagasaki differ markedly in mortality from liver cancer, possibly because of differential prevalence of hepatitis-B infection.

Biostatistics: Research continued on the development and evaluation of statistical methods useful in epidemiologic, clinical, and experimental studies of cancer. Statistical techniques for projecting the size of the AIDS epidemic were produced and applied to specific risk groups and subpopulations in the United States. A compartmental model was developed to evaluate the effects of screening for HIV and other interventions to retard the epidemic.

Study of various aspects of the analyses of multiple 2x2 tables and logistic models useful in epidemiologic studies were conducted. It was shown how pooling heterogeneous independent case-control studies affects the estimation of the common odds ratio and its estimated variance in balanced studies. Also, a new simple chi-square test of the plausibility of pooling was derived. Highly accurate sample size formulas for 2x2 tables were derived. These are particularly useful when the size of the control group may be a multiple of the case group. Methods previously formulated for accurate confidence limits for the odds ratio and ratio of proportions were extended to differences of proportions. The effects of cluster sampling of controls on standard methods of case-control analysis were examined and alternative analytical methods proposed. Weighted case-control sampling was investigated, in which the probability of selection for interview may depend both on case-control status and on other important covariates (e.g., smoking habits). Also studied was the efficient allocation of controls among strata for case-control studies in which the costs of finding and interviewing controls vary among strata.

In statistical research related to laboratory experimentation, methods for sparse data situations were studied, such as the analysis of the distribution of mutations induced in a gene of known sequence and the distribution of chromosome aberrations among bands. A multiple comparison procedure, which improves upon standard methods, was derived. Other statistical research involved the analyses of survival curves for cultured cells and confidence intervals for the parameters and their ratios in one-hit curves, particularly

as they relate to cell transformation studies. Statistical methods in population genetics included improved Bernstein's estimators for the human leukocyte antigen (HLA) system, as well as the study of linkage disequilibrium in such systems.

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 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 to which epidemiology can make a contribution, including those of immediate regulatory or public policy concern; and (2) stimulate the epidemiologic utilization of technical and data resources created by the Government for other purposes. Although many research and regulatory agencies are concerned with environmental causes of cancer, few have epidemiologic expertise. At this time of fiscal restraint, it is important to increase initiatives to develop and coordinate national data resources that, with proper safeguards, may be tapped for epidemiologic research. An example of such a resource is the registry of radiation workers, now under development by the Nuclear Regulatory Agency in response to a recommendation from the Program. The registry could be used to investigate the effects of low-level exposure to ionizing radiation.

Investigators in the Program continue to make extensive use of the National Death Index (NDI) established by the National Center for Health Statistics (NCHS). A project has been initiated to extend the NDI back for two or three years from 1979, its present initial year of coverage, as the costs would be prohibitively high to go further back in time.

Exploratory studies are underway to utilize data on occupational exposures and cancer mortality from several agencies, including the Social Security Administration (SSA), the Internal Revenue Service (IRS), the Bureau of the Census, and NCHS. Collaboration continued with the National Institute for Occupational Safety and Health (NIOSH) and with NCHS to expand the national vital statistics system to include occupational mortality. With the aid of the Census Bureau, coders from more than 30 states have been trained in coding the death certificate information on usual industry and occupation, and more than 20 states are submitting coded data to NCHS for review and tabulation. The file has grown from 270,000 records per year for 1984 to over 600,000 in 1988. Unfortunately, NCHS has been unable to secure long-term funding, so it is unlikely that the program will be extended beyond 1990.

Collaboration continued with the Office of the Assistant Secretary for Health in an effort to devise a legislative initiative to broaden access to the IRS address file beyond the present limitation to occupational studies. The initiative would also permit the IRS to transfer coded data on occupation to SSA in order to strengthen the Continuous Work History Sample (CWHS) as a data

base for studies of mortality in relation to exposures in the workplace. In the absence of legislative changes, staff members are exploring with SSA and IRS representatives the possibility of creating restricted-use tapes that could be provided to the Program in formats consistent with present regulations governing privacy and confidentiality. The change in the IRS agreement with NIOSH, under which current addresses are furnished to investigators involved in occupational studies (a change that allowed SSA to provide us with Social Security numbers needed for the IRS search), continues to benefit Program staff requiring current addresses for study subjects.

A methodologic study is underway to evaluate the utility of the SSA-CWHS as a tool for screening industry-of-employment cohorts for evidence of differential cancer mortality. A file of 90,000 deaths has been accumulated for the period 1973-1977, death certificates have been obtained from the states, and cause of death has been provided by NCHS. The file will be tested for its ability to reflect a number of well-known mortality differentials among industry-of-employment groups. In a collaborative study with IRS, its information on occupation of the taxpayer has been added to SSA information on industry-of-employment, death certificates have been obtained, and cause of death provided by NCHS. The IRS sample is under investigation to determine whether the IRS information on occupation will extend the usefulness of the SSA data on industry alone.

Research using Veterans Administration diagnostic indices of discharge increased during the year, together with research on record-linkage systems utilizing population-based cancer registries. This year, several investigations involved the participation of colleagues from other agencies,

including the Centers for Disease Control, NIOSH, Department of Energy, Environmental Protection Agency (EPA), National Oceanic and Atmospheric Administration, Department of Agriculture, and National Research Council.

International projects: During the year, staff members have been actively collaborating with Japanese scientists and others at the Radiation Effects Research Foundation to study the effects of ionizing radiation. Collaboration has taken many forms, from serving on advisory committees and attending workshops, to direct participation in the planning and conduct of projects in a number of countries around the world. The largest concentration of such collaborative studies is taking place in the Peoples Republic of China. Another international project is with the All-Union Scientific Center of Radiation Medicine in Kiev to plan studies of the health effects of the Chernobyl disaster of 1986.

Other activities: Within the Program, further steps were taken to improve the coordination of epidemiology and biostatistics components, to stimulate multidisciplinary activities linking epidemiologists with experimentalists, and to transfer etiologic developments to prevention activities in a timely manner. 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 with extramural investigators. In addition, several staff were involved with the preparation of comprehensive and critical reviews on a wide variety of topics. Service on interagency and other committees dealing with urgent public health and public policy issues was commonplace. A staff member serves on an advisory panel to

the Director, NCHS, on the operation of the NDI. Staff members served on an Office of Science Technology and Policy (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 the effects of indoor radon, the potential hazards to astronauts from space radiation, the prenatal effects of ionizing radiation, and the comparative carcinogenicity of radiation and chemicals; on advisory committees of the National Academy of Sciences dealing with the issues of indoor radon, the biological effects of ionizing radiation (BEIR V), and the effects of nuclear weapons tests in the Pacific. Staff members also contributed to departmental and interagency committees concerned with such issues as AIDS, asbestos, formaldehyde, Agent Orange, pesticides, water pollution, passive smoking, smokeless tobacco, ultraviolet radiation in relation to possible depletion of the ozone layer, and the use of epidemiology in risk assessment.

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 meet 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, studies of cancer-prone families, diet and nutrition, drug-related cancers, female cancers, epidemiologic methods, atomic bomb studies, specimen repositories, and emergent issues (e.g., AIDS). In-house committees continue to scrutinize and evaluate 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. In the aftermath of the formaldehyde study, which raised procedural questions, staff members developed guidelines to formalize mechanisms for undertaking and reviewing occupational, radiation, and other studies of a complex and sensitive nature. As a result, several ad hoc advisory committees of academic scientists have been formed to review and advise on potentially controversial studies carried out by the Program.

EXTRAMURAL PROGRAMS

The Extramural Programs Branch plans and manages a national extramural program of 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 and genetics, epidemiology, and special emphasis areas in AIDS-related epidemiology and biochemical epidemiology. Staff members keep abreast of scientific developments to identify specific areas of research that need to be stimulated, although most of the projects supported by the Branch are investigator-initiated.

The Branch continues to facilitate collaborative studies between epidemiologists and laboratory scientists. To achieve this aim, it reissued a request for cooperative agreement applications for research designed to develop, validate and apply laboratory-based biochemical markers of human exposure and susceptibility for use in cancer epidemiology. Eight new studies were funded from this initiative, including the following projects: the use of caffeine metabolite ratios for determining human exposure to compounds which induce cytochrome P450; determination of the frequency of nuclear DNA lesions,

ionizing radiation; studies of correlation between dietary aflatoxin intake to levels of excreted aflatoxin B_1-DNA adducts, oxidative metabolites in urine, aflatoxin M1 in human milk, and covalently bound aflatoxin to serum albumin; determination of excreted alkylated pyrines as markers of DNA alkylation in vivo in humans; and use of carnitine as a biochemical marker of fat intake. Investigators funded under this initiative meet annually to discuss progress.

The Small Grants Program for epidemiology was announced again in August 1988. The program is serving a useful purpose, especially for young investigators, recruiting doctoral students, fellows and junior faculty into cancer epidemiology. Awards are intended to support initiatives that focus on: (1) planning a complex study; (2) developing or validating a laboratory or statistical procedure that may be applied to cancer epidemiologic research; or (3) analyzing previously collected data, including meta-analysis. This year, peer review of these applications was conducted by telephone conference, a process well-received by reviewers and applicants, while saving travel costs.

The Branch continues to encourage investigations of the incidence and etiology of malignancies associated with AIDS and HIV infection. A Request for Applications (RFA) was reissued this year for research on the relationship of certain cancers or precursor states to immune status, genetic factors, HIV strains, co-infection with other viruses, and AIDS treatments. Studies resulting from this initiative include a record-linkage project to clarify the incidence of malignancies among AIDS patients in San Francisco, an evaluation of the Epstein-Barr virus in lymphoproliferative disease among HIV-infected children, and a study of malignancies occurring in a cohort of homosexual men. The Branch also supports studies of lymphomas occurring in HIV-infected individuals and risk factors for Kaposi's sarcoma, and plans annual meetings of investigators conducting research on HIV-associated malignancies. A large-scale collaborative study with the National Institute of Allergy and Infectious Diseases has continued to provide valuable data to clarify the natural history of AIDS.

The transfer of epidemiology grants from the Organ Systems Program resulted in an increment of 17 projects and one program project, an 11% increase in the number of grants monitored by the Branch. Most of these grants (14) are in the field of breast cancer.

A workshop was held with investigators involved in studies of obesity and cancer in women, with most of the projects stimulated by an earlier RFA issued by the Branch. The stage was set for participation in a multi-Institute meeting on measurement and significance of variation in body fat distribution to be held in September 1989. Preliminary findings from NCI-reported studies suggest that body fat distribution is significantly related to risk of breast and endometrial cancers, to testosterone/estrogen ratios, and to levels of free estradiol.

The Branch continues to support the congressionally-mandated Small Business Innovative Research Program designed to stimulate small business participation in Federal research and development projects. Toward this end, the Branch has worked closely with intramural staff to develop concept statements for activities suitable for epidemiology, statistics, genetics, and related multidisciplinary areas.

PROSPECTS

It is difficult to project activities over time, given uncertainties in positions and funding, and in the direction that new findings and opportunities may lead. Nevertheless, we will continue 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 resolve seminal questions in cancer epidemiology and biostatistics. Emphasis will be given to in-depth analytical studies to identify etiologic agents and elucidate mechanisms of carcinogenesis. Continued efforts will be made to utilize, in an efficient and effective manner, resources of the NCI and other Federal agencies.

Staff members will continue 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. The Program is constantly challenged to increase the scope of its extramural and cooperative research and to help develop Institute and Federal programs and policy in all areas related to cancer epidemiology, including etiology and prevention.

After a period of substantial growth over the past decade, the size of the intramural epidemiology program has stabilized. Yet, there remains a need to maintain a capability to analyze descriptive data on cancer statistics, such as those provided by the SEER program and the NCHS (e.g., for development of the cancer maps), to generate and formulate etiologic leads to cancer. It is clear that the major emphasis of the Program should be on analytical epidemiologic studies to pursue etiologic clues, and to identify the lifestyle and other environmental and host factors that pose carcinogenic risks in humans. If new funds and personnel should become available, additional priority will 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 and innovative ways of measuring exposures. In assessing lifestyle and other environmental risk factors, greater emphasis will be placed on epidemiologic studies that incorporate biochemical and molecular probes of exposure, response, susceptibility, and mechanisms of action. Studies of cancer-prone families and genetic syndromes provide exceptional opportunities to apply new molecular techniques, including those related to expression of human oncogenes and genetic-environmental interactions. Genetic epidemiology will be an area of increasing emphasis in efforts to keep pace with the dramatic progress being made in molecular genetics. The AIDS epidemic and associated neoplasia 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 retroviruses. 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 and complex. With the development of new experimental probes, their application in biochemical and molecular epidemiology represents a strategy that will help clarify key issues in cancer etiology and prevention.

will be given to understanding reasons for geographic, temporal, and racial/ethnic variations in cancer incidence and mortality. Toward this end, studies of minority groups will be given renewed emphasis. Attention will also be given to the study of relatively neglected or uncommon neoplasms, involving collaborative case-control studies in several areas or centers, often utilizing the network of SEER registries. Whenever possible, data from epidemiologic studies will be used for methodologic evaluation and development, for investigation of carcinogenic mechanisms of action, and for research into quantitative risk assessment. The staff will continue to provide epidemiologic and biostatistical support to a wide variety of groups involved in efforts to understand and control cancer. The effectiveness of intramural and extramural initiatives will depend upon our success in promoting interaction and coordination with the other segments of the National Cancer Program. Special efforts will be made to interact more closely with DCPC staff to enhance the flow of ideas from etiologic research to intervention studies, in concerted efforts to develop preventive measures and reduce the toll of cancer as quickly as possible.

ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

The major functions of the Biostatistics Branch are to conduct independent and collaborative investigations, using biometric approaches, into the distribution and determinants of cancer in individuals and populations; to develop and evaluate statistical methods for the design, conduct, and analysis of epidemiologic, experimental and clinical studies of cancer; 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; 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.

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. Activities are listed according to section, although often members of several sections are involved in individual projects.

Mathematical Statistics and Applied Mathematics

Activities of the Mathematical Statistics and Applied Mathematics Section are principally concerned with research in statistical methods useful in cancer research and collaboration in the conduct of cancer studies with other branches and laboratories both within and outside the Division of Cancer Etiology (DCE).

Research continued on various aspects of the analyses of multiple 2x2 tables and logistic models useful in epidemiologic studies. It was shown how pooling heterogeneous independent case-control studies affects the estimation of the common odds ratio and its estimated variance in balanced studies. Also a new simple chi-square test of the plausibility of pooling was derived. A logistic model was used to derive simple tests for comparing hospital and neighborhood controls in individually matched studies. Highly accurate sample size formulas for 2x2 tables were derived. These are particularly useful where the size of the control group may be a multiple of the case group. Methods previously formulated for accurate confidence limits for the odds ratio and ratio of proportions were extended to differences of proportions.

In statistical research related to laboratory experimentation, methods for sparse data situations such as the analysis of the distribution of mutations induced in a gene of known sequence and of chromosome aberrations among bands were studied. A multiple comparison procedure which is a considerable improvement over standard methods was derived. Other statistical research involves the analyses of survival curves for cultured cells and confidence intervals for the parameters

and their ratios in one-hit curves, particularly as they relate to cell transformation studies.

Statistical methods in population genetics include improved Bernstein's estimators for the human leukocyte antigen (HLA) system as well as the study of linkage disequilibrium in such systems. Study of the statistical analysis of Gm immunoglobulin allotype data continues.

In screening studies a mathematical model was constructed which provides a strong theoretical basis for the statistical analysis of a breast cancer screening study.

Several of the novel statistical procedures described above as well as others involving permutational algorithms have been incorporated into computer programs.

Collaboration continues with investigators both within and outside DCE. This includes statistical collaboration on studies of the possible association of HLA type with response to HIV infection, of HIV seroprevalence in blacks in New York, fecal mutagenicity and colorectal cancer, multiple myeloma and HLA type, Gm and Km immunoglobulin allotyping in nasopharyngeal carcinoma in Malaysia, non-Hodgkin's lymphoma and bladder cancer in dogs, long-term effects of radiation exposure and stable chromosome aberrations in humans, DNA repair defects in Cockayne syndrome patients, and radiation and thyroid cancer in rats. Work outside of NCI includes a study of HLA type and obesity, the analyses of a FDA radiation study on dogs in Colorado, and a Korean study of the possible protective effect of ginseng intake on cancer risk.

Epidemiologic Methods

The Epidemiologic Methods Section conducts research 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.

Work continues on the design and analysis of case-control studies. In collaboration with staff at the National Institute of Child Health and Human Development (NICHD), Branch staff have studied the effects of cluster sampling of controls on standard methods of case-control analysis and have proposed alternative analytical methods. Such cluster samples could arise, for example, in telephone surveys of controls. In collaboration with staff at the National Institute of Environmental Health Sciences (NIEHS), Branch staff have submitted a manuscript on weighted case-control sampling in which the probability of selection for interview may depend both on case-control status and on some other important covariates, like smoking status. In addition, Branch members are studying efficient allocation of controls among strata for a case-control study in which the costs of finding and interviewing controls vary among strata.

One staff member collaborated with staff in the Division of Cancer Prevention and Control (DCPC) to organize a workshop on the impact of errors in measurements of the reliability of epidemiologic studies. Branch members have served

as editor and reviewers of papers presented at this conference, and the proceedings are in press.

A manuscript was completed on projecting cancer risk for individuals with specific risk factors and for populations. This risk model for projecting individualized breast cancer risk was developed in collaboration with staff in DCPC. One staff member has studied exposure to radon in the home as a risk factor for lung cancer, taking complex temporal relationships into account. Fitted risk models predict that nearly 3,800 lung cancer deaths annually are associated with exposures above EPA's radon "action level." Another paper considers variance calculations for risk projections from cohort data. These methods, which have been applied to projecting the risk of recurrence following resection of lung cancer, allow one to assess the uncertainties associated with random error and systematic model misspecification. One manuscript has been published and one has been submitted on the problem of calculating confidence intervals for attributable risks based on logistic modelling of exposures and confounders.

Staff members worked on aspects of the design and analysis of occupational cohort studies. A manuscript, written in collaboration with Professor Siemiatycki of McGill University, gives empirical evidence that reliable inference on occupational exposure is often obtained even in the absence of data on potential confounders. Other work, done in collaboration with members of the Environmental Epidemiology Branch, indicates that failure to control for smoking status will rarely distort relative risks in occupational studies by more than 30 percent. Work has been published on alternative variance calculations for analyzing and designing economical case-cohort studies, and a manuscript is in preparation on selecting efficient designs for obtaining exposure information from a large assembled cohort.

Detailed statistical methods on "back calculation" for projecting the size of the acquired immunodeficiency syndrome (AIDS) epidemic were published, and rapid regression methods were developed that permit a more realistic assessment of random and systematic uncertainties in such projections. These methods are being applied to specific risk roups and subpopulations in the United States, in collaboration with members of the Environmental Epidemiology Branch. These calculations require neither assumptions on the seroprevalence of human immunodeficiency virus (HIV) infection nor on the proportion of seropositives who will develop AIDS, and provide a useful complement to projections based on simple extrapolation. In collaboration with staff of the Radiation Epidemiology Branch, a compartmental model has been developed and published to evaluate the effects of screening for HIV and other interventions to retard the epidemic. Other areas of active methodologic research and development include computer programs for epidemiologic analysis with the IBM-PC, adaptation of SAS procedures to analyze case-cohort data and other complex survival data, and methods for comparing diagnostic tests.

Collaboration within the Epidemiology and Biostatistics Program was extensive. Section staff were involved in a reassessment of thyroid cancer risk in six cohorts exposed to low doses of ionizing radiation. Risks from solar UV radiation were also examined. Further commentary appeared describing secular trends in UV radiation at eight monitoring locations. Collaboration continued to quantify risks of early menopause following radiotherapy and/or chemotherapy for cancer. Included in AIDS research was a cohort study of high-risk mothers and infants and a cohort study of hemophiliacs. Section members also participated in

the design and analysis of several studies of cancer in China (see Analytical Studies).

Collaboration with groups outside DCE also continued during the year. One member serves as Chairman of the Operations Committee that monitors the progress of a placebo controlled clinical trial of azidothymidine, sponsored by the Veterans Administration, among patients with AIDS-related complex, and he has been asked by the Veterans Administration to assist in designing a vaccine trial for AIDS. Other AIDS-related projects involve collaborations with faculty at Johns Hopkins University. In collaboration with the staff at the University of California at Los Angeles (UCLA), one member has written three papers to describe the interactive effects of joint exposures to carcinogens in rodent assays. One member is collaborating with staff at the Univeristy of Paris to develop methods of inference for estimates of absolute risk derived from population-based case-control studies. Models for projecting risk for breast cancer for women with several known risk factors have been refined with collaborators in DCPC. Consultation has also continued with DCPC staff on the design of large-scale interventions to reduce smoking. Work is proceeding in collaboration with staff at NIEHS on alternative methods of analysis for population-based case-control studies.

Analytical Studies

The Analytical Studies Section conducts investigations to generate and evaluate hypotheses regarding the causes of cancer in human populations. Members of this and other sections of the Branch often work collaboratively with scientists in other institutions in the United States and abroad to gather and analyze epidemiologic data to assess environmental and host determinants of cancer.

Analyses of cancer incidence and mortality: Evaluations of the variation in cancer rates over space and time can often provide leads to etiologic factors. This year cohort analyses were conducted of the changing age-specific rates of several cancers from the 1950s to 1980s. Trends for oral, esophageal and laryngeal cancer mortality were shown to be quite similar, but the patterns differed markedly between males and females and whites and nonwhites. Noteworthy were rising trends for all three cancers among black males, which compared with relatively stable rates for white males (although some decline in oral and laryngeal rates was detected among later-born cohorts). In contrast, the trends for females showed declining, then rising, then falling rates. Lung cancer trends were also examined. The end of the epidemic rise in age-adjusted rates of this cancer among males is nearing, with a nearly 30% decrease in lung cancer death rates among white males under age 45 between the mid-1970s and mid-1980s, a reflection of a reduced prevalence of smoking. Recent declines in the mortality rates for lung cancer among nonwhite men and among white and nonwhite females below age 45 were also reported.

Collaborative case-control and cohort studies in the United States: The Branch undertakes collaborative analytical investigations to identify and quantify risk factors for cancer. In the largest investigation of oral and pharyngeal cancer yet conducted, section staff have worked with scientists in Atlanta, New Jersey, Los Angeles, and the San Francisco area in the design and conduct of a population-based case-control study. Published during the year were results of analyses of interview data from nearly 1,200 cancer patients and 1,300 controls, which showed smoking and drinking to be the dominant risk factors. The large study

size enabled the first clear demonstration of effects of alcohol consumption among lifelong nonsmokers and indicated that smoking and drinking tended to combine more in a multiplicative than additive fashion in affecting oral cancer risk. Risks of oral/pharyngeal cancer were shown to fall sharply following cessation of smoking. Smokeless tobacco was also implicated as a risk factor among nonsmokers, although the numbers of users were too small for detailed analyses of the relative influences of snuff vs. chewing tobacco. Dietary analyses of oral cancer risk showed significantly protective effects associated with high fruit intake, with those in the highest quartile of consumption at less than half the risk of those in the lowest.

Tobacco and alcohol were also found to be the principal determinants of esophageal cancer in coastal South Carolina, where rates of this tumor have long been elevated among blacks. Results published during the year from this case-control study conducted with the Medical University of South Carolina revealed that consumption of local moonshine whiskies, reported by nearly 90% of the black male patients interviewed, appears to be responsible, at least in part, for the clustering. Higher risks were independently associated with poor nutrition, providing further evidence of a dietary component in the etiology of esophageal cancer and additional clues to its higher rates among blacks than whites. Interviewing continued during the year for another case-control investigation of esophageal cancer. Nearly 600 patients and more than twice as many population-based controls in Atlanta, Detroit, and New Jersey will be enrolled in this collaborative study focusing on differences in exposures and risks between blacks and whites. Utilizing the same control series for comparison, patients with cancers of the pancreas and prostate and multiple myeloma are also being enrolled. Each of these cancers occurs more frequently in blacks than whites for as yet unknown reasons.

Data analyses continued on two large population-based case-control studies: the national bladder and skin cancer surveys. Both surveys were conducted in the late 1970s, but provide data from nearly 19,000 interviews on population exposures and risk factors for these tumors that are still applicable today. The contribution of occupational exposures to bladder cancer risk was explored during the year, with best estimates of the attributable risk of "high-risk occupations" placed at about 20% among males and about 5% among females. The relative risks of occupational bladder cancer were similar in men and women, although the rate of exposure to occupational carcinogens was substantially lower in women. Occupational bladder cancer among nonwhite men was similar to that among white men. There was, however, some evidence of risk differences between whites and nonwhites that appeared to be due to racial differences in exposure among men within the same industry and job title. These data also provide for the most definitive evaluation of the relation of cigarette smoking to bladder cancer risk. Clear trends were observed with duration and intensity of smoking, with detection, for the first time, of a rapid reduction in risk within a few years of quitting smoking. This pattern was seen both in the U.S. and in Italy, where case-control data also showed markedly higher bladder cancer risk associated with smoking black compared to blond tobaccos. The increased carcinogenic potential of the black tobacco is further suggested by the detection of hemoglobin adducts to 4-aminobiphenyl (a bladder carcinogen) in the blood of smokers of black tobacco.

A case-control study of lung cancer involving 996 cases and 1085 controls in the Teamsters Union was conducted to determine whether diesel-exposed truck drivers

and others employed in diesel-exposed jobs have excess lung cancer as was previously reported for bladder cancer. It was found that long-term truck drivers who were potentially exposed to diesel exhaust have about a 50 to 90% increased lung cancer risk, after control for smoking. The actual level of diesel exposure among truck drivers is unknown, however, and industrial hygiene studies within the trucking industry are currently underway under the NCI/NIOSH Interagency Agreement.

Field work neared completion in case-control studies of biliary tract cancer in collaboration with the University of Southern California (USC) and renal pelvis cancer in collaboration with USC, the New Jersey Department of Health, and the University of Iowa. The latter investigation was prompted by an earlier Branch study in Minnesota, which revealed an association between renal pelvis cancer and long-term use of acetaminophen-containing analgesics. The finding was based on small numbers of observations, but is of concern because of a recent report of carcinogenicity in an animal experiment with this commonly used medication. Data from the Minnesota study published this year showed that use of diuretics was associated with increased renal adenocarcinoma risk, consistent with a similar finding from Los Angeles published last year. The biliary cancer study is one of the few etiologic investigations of this relatively rare tumor.

Cohort analyses to investigate dietary factors in cancer risk continued 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. Work this year extended the mortality follow-up through 1984. Indices for intake of fiber, folate, and several nutrients have been created, and analyses of risks for several cancers (stomach, pancreas, prostate) are continuing.

The Branch has a major role in the National Mortality Followback Survey (NMFS) in collaboration with the National Center for Health Statistics (NCHS). The survey involves the administration of a mail questionnaire to the next-of-kin of 20,000 decedents or about 1% of the deaths occurring in the U.S. in 1986. Among other issues, the survey will evaluate risk factors such as diet, use of tobacco, alcohol and hormones, disease history, and occupation and their relationship to several rare cancers. Questionnaires have been received for over 500 deaths due to cancer of the small intestine, and from 100 to 200 deaths from male breast cancer, liver cancer among young women, oral cancer among young men, and cancers of the thymus, adrenal, and pituitary glands. Collaborative methodologic studies on various aspects of the mail questionnaire study design have been completed as part of the pretest for the NMFS.

In collaboration with the Radiation Epidemiology Branch and the U.S. Children's Cancer Study Group (CCSG), a case-control study evaluating low frequency electromagnetic radiation in relation to childhood leukemia has begun. The study has been grafted upon a nationwide CCSG investigation into the environmental and host determinants of childhood leukemia. In a cohort study of mortality among 250,000 U.S. veterans administered a brief questionnaire in the 1950s, mortality from adult leukemia, particularly myeloid leukemia, was shown to be increased among smokers, confirming reports from other studies that leukemia is a smoking-related cancer.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that 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 have been conducted in these investigations.

In Shanghai, smoking was shown to be 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 were nonsmokers, however, so other factors account for their high rates. What these factors are remain to be clarified, but a clue arises from the observations of increased risk among women reporting greater frequencies of high temperature wok cooking, increased house smokiness and eye irritation when cooking, and greater use of rapeseed cooking oils. The link to rapeseed oil is intriguing since rapeseed volatiles have been reported to be mutagenic in the Ames test. Initial results from analyses at NCI's Laboratory of Human Carcinogenesis confirm reports from China of mutagenic activity of rapeseed oil volatiles, with further characterization of the oils now underway. Occupational analyses revealed a lowered risk of lung cancer among workers in the cotton textile industry, a major employer in Shanghai. The finding is consistent with reports from the U.S., and raises the possibility of exposure to protective agents (e.g., endotoxins) in the work environment.

In Shenyang, cigarette smoking also was a strong risk factor, with a higher prevalence of smoking among females compared to elsewhere in China contributing to the area's high rates. Air pollution was also a significant factor, with risk rising in proportion to exposure to indoor pollutants from coal-burning Kang and other home heating devices. Occupational determinants were also found, with a 3-fold increased risk of lung cancer among workers in one of China's largest copper smelters and among males living within 1 km of the smelter's central stacks.

In Shandong, dietary differences distinguished cases and controls. The stomach cancer patients preferred and consumed more salted foods and more of the local favorite sour pancakes, and significantly less fresh vegetables. The most marked protective effects were for vegetables of the allium class, including garlic, of note because of the tumor-inhibitory properties of allium reported from experimental studies. To follow-up on these leads and evaluate whether diet similarly affects the origins of precancerous lesions (chronic atrophic gastritis, dysplasia) of the stomach, additional research was launched during the year in Shandong. Three thousand adults in this high-risk area are being enrolled in a screening program to detect early cancers and to compare questionnaire items and biochemical markers between those with various precursor lesions. They will then be followed to directly evaluate rates of transition to more advanced states, including gastric cancer.

In the Linxian case-control study, consumption during adulthood of pickled vegetables was not found to be the strong risk factor it was suspected to be. Intake of pickled vegetables in either the 1950s or 1970s was not higher among the esophageal cancer patients, nor was intake of fresh fruit and vegetables lower. Instead, the cases were characterized by lower fluid and higher wheat and corn intake, similar to the Caspian littoral of Iran where clusters of high esophageal cancer rates have also been found.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,400 persons with esophageal dysplasia. 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 a one-half replicate of a 2^4 factorial design, is used for the general population trial. A brief questionnaire was administered and 5 ml serum obtained from each participant prior to enrollment. The studies, now in their fourth and third years, respectively, 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. Assays of nitrosamines in urine specimens collected from trial participants are planned to assess whether N-nitroso compounds may be involved in the carcinogenic process. Increases in cell proliferation, based on tritiated thymidine labelling assays performed at the Memorial Sloan-Kettering Cancer Center, were found among Linxian residents with histologic evidence of dysplasia.

Additional collaborative research in China was conducted during the year, including cohort studies evaluating the cancer experience of occupational groups exposed to benzene, silica, radon and arsenic. The benzene study is enrolling 100,000 workers to enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. During the year benzene air level measurement and other exposure data since 1949 or thereafter were collected from 700 factories in 12 cities. Cohort follow-up has begun, and plans for a nested case-control study of leukemia developed. The silica study will assemble 10,000 persons in central China with silicosis, plus 50,000 persons heavily exposed to silica without silicosis, for evaluation of this agent that has been recently shown to initiate and promote cancer in experimental animals. The radon/arsenic study focuses on nearly 30,000 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.

A case-control study of stomach cancer, in collaboration with the Center for the Study and Prevention of Cancer in Florence and other Italian institutions, was conducted to investigate reasons for the high risk of this cancer in north and central parts of Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Analyses of interview data from 1,000 cancer patients and 1,100 controls, completed during the year, revealed strong dietary associations. Increased risks were associated with certain traditional soups and meats, while decreased risks were linked to intake of fresh fruits and vegetables. Protective effects were also associated with garlic consumption.

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. Recently, an increased risk of male breast cancer has been found in workers employed in the formulation of estrogenic creams, and an elevated risk of malignant melanoma has been uncovered among printers exposed to unrefined lubricating oils. Other analyses have identified new occupational leads for bladder cancer, multiple myeloma, and leukemia. Plans were also formulated this year for the conduct of a collaborative case-control study of renal cancer in Sweden, Denmark, Germany, Australia, Shanghai and the United States.

Information Resources Management

The Branch is responsible for assuring delivery of computer-related support to epidemiologists and biometricians throughout the Epidemiology and Biostatistics Program. The major recurring activities of the Information Resources Management Section include contract procurement and administration, information management and dissemination, as well as technical and consultative support to investigators in the program. This year the major challenge faced by the Section was maintaining the high quality of computer support and services provided to the Program while containing their cost.

Individual staff members continued to provide support to new as well as on-going projects. Several noteworthy collaborations include: 1) updating population and mortality rate files with the latest available data from the Census Bureau and the NCHS, 2) extending the use and capabilities of a biospecimen inventory system that facilitates the management of biospecimen materials, and 3) reviewing alternative record linkage systems to evaluate their quality and cost effectiveness for cohort matching.

Summary Report

Biostatistics Branch

Progress on Research Contracts

The Branch's research contracts (FY-89 expenditures $1,015,00) 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 rate areas and in heavily exposed populations in China, collaborative contracts have been negotiated with the Chinese Academy of Medical Sciences (CAMS), the Liaoning Province Public Health Station (LPPHS), the Chinese Academy of Preventive Medicine (CAPM), and the Beijing Institute for Cancer Research (BICR). Contracts (CP-41019 and CP-95616) enable the conduct of a 5-year randomized intervention trial in Linxian to test whether vitamin/mineral supplementation can lower the incidence of esophageal cancer, which occurs more commonly in this rural county than elsewhere in the world. Over 33,000 persons are enrolled and monitoring of their cancer experience continues. An additional CAMS contract (CP-85640) funds studies of silica- and radon/arsenic-exposed workers, with data collection ongoing during the year. The LPPHS investigation (CP-51021) in Sheyang, one of China's most heavily polluted cities, this year involved analysis of data from interviews completed last year with lung cancer cases and population controls. Contract CP-85641 with the CAPM supports a cohort survey evaluating risks from benzene among approximately 100,000 workers in 12 Chinese cities. Air monitoring data from factories were obtained during the year and used to classify workers according to benzene exposure, and follow up for mortality is underway. A contract with the BICR (CP-95660) initiated this year enables the conduct of a survey of 3,000 high-risk subjects to classify gastric lesions, identify their determinants, and chart changes to cancer over time.

A multicenter study of stomach cancer is ongoing in collaboration with the Preventive Oncology Center of Florence, Italy (CP-51010). Enrollment of cases and controls, interviewing and biologic specimen collection in two high-risk (Firenze, Forli) and two low-risk (Genova, Cagliari) areas was completed during the year, and dietary contributors to the substantial variation in gastric cancer in Italy are being evaluated.

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). Data collection was completed for 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-89

Institution/Principal Investigator Contract Number	Title
Chinese Academy of Medical Sciences Dr. Li Bing NO1-CP-41019 & 95616	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
Chinese Academy of Medical Sciences Dr. Li Jun Yao NO1-CP-85640	Epidemiologic Studies of Cancer in China
Chinese Academy of Preventive Medicine Dr. Yin Songnian NO1-CP-85641	An Epidemiologic Study of Benzene Exposure in China
Beijing Institute for Cancer Research Dr. You Wei-cheng NO1-CP-95660	Precancerous gastric lesions: study of their determinants and rates of transition in a population in China at high risk of stomach cancer

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04265-24 BB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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:	R.E. Tarone	Mathematical Statistician	BB	NCI
	H.M. Pettigrew	Mathematician	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
R.E. Tarone	Mathematical Statistician	BB	NCI
H.M. Pettigrew	Mathematician	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

Dr. Gart and Mr. Nam are collaborating with Dr. Goedert of the Environmental Epidemiology Branch and Dr. Mann of the Laboratory of Viral Carcinogenesis on a study of the possible association of the response to HIV I and II with the HLA genetic system in man.

Dr. Tarone provided statistical advice to various members of the Environmental Epidemiology Branch's Viral Epidemiology Section. He advised Dr. Robert Biggar on testing for differences in malaria antibody titres between EBO antibody negative and EBO antibody positive individuals. He advised Ms. Elizabeth Maloney regarding the use of Gm immunoglobulin allotypes to assess the degree of racial admixture in South American Indians. He assisted Dr. Paul Levine and Ms. Ruth Maloof in determining sample sizes for a HIV seroprevalence study of blacks residing in New York to compare prevalence rates of individuals born in the United States to those born in Haiti and those born elsewhere in the Carribean region.

Dr. Pettigrew completed his collaboration with Dr. Mark Schiffman of the Environmental Epidemiology Branch on projects involving fecal mutagenicity and colorectal cancer. He is a co-author of two papers reporting the results.

Dr. Gart and Mr. Nam are collaborating with Dr. Linda Pottern of the Environmental Epidemiology Branch on the statistical analysis of a case-control study of multiple myeloma with regard to the possible association of the disease with the HLA genetic system.

Dr. Tarone continues to collaborate with Dr. Paul Levine of the Environmental Epidemiology Branch on a study of Gm and Km immunoglobulin allotypes in nasopharyngeal cancer patients from Malaysia. He has completed the statistical analysis and is preparing a manuscript reporting the results of the study.

Dr. Tarone continues to collaborate with Dr. Joseph McLaughlin of the Biostatistics Branch on a case-control study of renal cancer, with particular emphasis on determining if diuretic use increases the risk of renal cancer.

Dr. Tarone is collaborating with Dr. Howard Hayes and Dr. Kenneth Cantor of the Environmental Epidemiology Branch on a case-control study of non-Hodgkin's lymphoma and bladder cancer in pet dogs. The study is designed to evaluate possible relationships between exposure to environmental agents such as herbicides and pesticides and cancer risk.

Dr. Tarone is collaborating with Dr. John Boice and Ms. Ruth Kleinerman of the Radiation Epidemiology Branch on studies of the long-term effects of radiation exposure on the frequency of stable chromosome aberrations in human populations. A paper quantifying the increased incidence of stable aberrations existing 30 years after treatment with very high doses of ionizing radiation for cervical cancer has been accepted for publication. A paper summarizing the effects of lower doses in patients treated for thymic enlargement or for lymphoid hyperplasia of the nasopharyngeal apparatus and in tuberculosis patients exposed to multiple fluroscopic examinations is in preparation.

Dr. Gart is advising Dr. Beebe of the Clinical Epidemiology Branch on the application of his methods for finding confidence limits for the ratio of proportions to a problem of adjusting liver cancer death data for both over- and underreporting on the death certificate.

Mr. Thomas continues to provide computer support, advice, and assistance in the use of microcomputers to various members of the section. He recommends purchase of appropriate hardware and software when necessary as cost effective tools to further the research and consulting efforts of the section. Several additional microcomputer systems were added this year which facilitate the development, use, and sharing of software in this section which is often requested by other researchers throughout the world.

Mrs. Smith continues to provide mainframe computer support for several of the projects reported here as well as using microcomputers when appropriate.

Division of Cancer Etiology - Other Programs

Dr. Tarone continues to collaborate with Dr. Kenneth Kraemer of the Laboratory of Molecular Carcinogenesis and Ms. Susanna Barrett of the Division of Cancer Biology's Dermatology Branch on experiments to identify the DNA repair defect in cultured cells from Cockayne syndrome patients by measuring their capacity to repair UV-irradiated plasmids. He also advised Dr. Kraemer on the statistical analysis of plasmid mutation assays in cultured cells from patients with Bloom's syndrome.

Dr. Pettigrew continued to advise Dr. Raymond Gantt of the Radiation Effects Branch on the results of an NCI review of pathology specimens from an experiment conducted by the Food and Drug Administration to study the relative effectiveness of 131-I and X-rays in producing thyroid cancer in rats.

Dr. Tarone continues to collaborate with Dr. Katherine Sanford of the Laboratory of Cellular and Molecular Biology on experiments to elucidate the mechanisms of increased susceptibility to chromosome damage in cultured cells from patients with cancer-prone disorders. He is collaborating with Dr. Sanford and Dr. Kenneth Kraemer of the Laboratory of Molecular Carcinogenesis in a study of abnormal chromosomal radiosensitivity in cells from xeroderma pigmentosum heterozygotes.

Dr. Tarone assisted Dr. Henry Hennings of the Laboratory of Cellular Carcinogenesis and Tumor Promotion in the statistical analysis of skin painting experiments performed to determine if application of cis-platin leads to increased conversion rates.

Dr. Pettigrew will assist Dr. Carl E. Smith of the Chemical and Physical Carcinogenesis Branch to review data collected under NCI contracts by the late Dr. Albert Segaloff of the Alton Ochsner Clinic.

Division of Cancer Biology and Diagnosis

Dr. Tarone continues his collaboration with Dr. Jay Robbins and others in the Dermatology Branch in experiments to study the *in vitro* sensitivity of cultured cells from patients with cancer-prone diseases and primary neuronal degenerations after exposure to DNA-damaging agents. He is collaborating with Dr. Robbins and Dr. Lana Seguin of the Dermatology Branch in a study of UV-induced chromosomal aberrations in patients with the variant form of the skin cancer-prone disease xeroderma pigmentosum.

Dr. Tarone advised Dr. Hayden Coon of the Laboratory of Genetics on the analysis of odorant responses in cell cultures of neuroblasts from rat olfactory epithelium.

Dr. Pettigrew consulted with Dr. Jeffrey L. Medeiros of the Laboratory of Pathology on the analysis of survival data of patients with lymphoid tumors classified as to histology and immunology.

Mr. Thomas revised his life table computer program to facilitate this ana

Division of Cancer Treatment

Dr. Tarone is collaborating with Dr. Vilhelm Bohr of the Laboratory of Molecular Pharmacology and Dr. Michelle Evans of the Medicine Branch in experiments designed to quantify differences among xeroderma pigmentosum complementation groups in their abilities to perform DNA repair in the actively transcribed regions of the genome.

Dr. Tarone provided assistance to Dr. Albert Fornace of the Radiation Oncology Branch on the statistical analysis of in vitro cell survival experiments to determine if cell lines constructed to produce high amounts of metallothionein could better tolerate exposure to DNA-damaging agents. Dr. Tarone also assisted Dr. Fornace in the analysis of experiments to determine if heat shock-induced B2 RNA polymerase III differed from constitutively produced B2 RNA polymerase III in the location or frequency of mutations.

Dr. Tarone completed collaboration with Dr. Eddie Reed of the Clinical Oncology Program on studies of testicular cancer patients treated with cis-platin. A paper was published reporting a direct association between prognosis and the level of cis-platin DNA adducts in peripheral blood.

Other Parts of NIH

Dr. Gart and Mr. Nam completed their collaboration with Mr. Fabsitz of the National Heart, Lung, and Blood Institute on the association of a particular HLA type with obesity. A paper summarizing the result is being published.

Other Activities

Dr. Pettigrew assisted Dr. Richard Chiaccherini of the Center for Devices and Radiological Health, FDA, concerning a long-term study of beagle dogs exposed to ionizing radiation being conducted at Colorado State University. He participated in a site visit to Ft. Collins, Colorado, and advised on methods of data management and analysis.

Mr. Nam collaborated with Dr. Taik Koo Yun of the Korea Cancer Center Hospital in a case-control study to investigate possible reduction of cancer risk by ginseng intake.

Publications:

Chu KC, Smart CR, Tarone RE. Analysis of breast cancer mortality and stage distribution by age for the HIP clinical trial. JNCI 1988;80:1125-32.

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Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. N Engl J Med 1988;318:1633-7.

Levine PH, Blattner WA, Clark J, Tarone R, Maloney B, Murphy EM, Gallo RC, Robert-Guroff M, Saxinger WC. Geographic distribution of HTLV-I and identification of a new high-risk population. Int J Cancer 1988;42:7-12.

Potter M, Sanford KK, Parshad R, Tarone RE, Price FM, Mock B, Huppi K. Genes on chromosomes 1 and 4 in the mouse are associated with repair of radiation-induced chromatin damage. Genomics 1988;2:257-62.

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Sanford KK, Parshad R, Gantt R, Tarone RE, Jones GM, Price FM. Factors affecting and significance of G_2 chromatin radiosensitivity in predisposition to cancer. Int J Rad Biol (In Press).

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Schiffman MH, Van Tassell RL, Robinson A, Smith L, Daniel J, Hoover RN, Weil R, Rosenthal J, Nair PP, Schwartz S, Pettigrew H, Curiale S, Batist G, Block G, Wilkins TD. Case-control study of colorectal cancer and fecapentaene excretion. Cancer Res 1989;49:1322-6.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04267-24 BB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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:	R.E. Tarone	Mathematical Statistician	BB	NCI
	H.M. Pettigrew	Mathematician	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 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 human leukocyte antigen (HLA) data.

PROJECT DESCRIPTION

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

J. J. Gart	Chief, MSAMS	BB	NCI
R. E. Tarone	Mathematical Statistician	BB	NCI
H. M. Pettigrew	Mathematician	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 derived several general results regarding the effect of pooling stratified or independent case-control studies. When the stratification is meaningful and the sample sizes are balanced, it is shown how the pooled measures of association, such as the odds ratio, are affected. When stratification is necessary, the estimated variance of the pooled estimator is shown, in general, to be larger than that of the stratified estimator. Additionally simple chi-square tests of the need to retain the stratification in the analysis are derived.

John J. Gart has found improved methods for finding confidence intervals for the parameter in a one-hit curve as well as for ratios of such parameters. In a paper to be published shortly the methods are applied to chemically-induced cell transformation curves enhanced by radiation.

John J. Gart has completed his research on statistical tests for comparing hospital and neighborhood controls in doubly matched case-control studies. The tests are versions of McNemar's statistic and the usual chi-square test for the two-by-two table or combinations thereof. A paper reporting the results has been submitted for publication.

John J. Gart has derived improved versions of sample size formulas for tests comparing two proportions by Fisher's exact test. An arcsine version is found to be the most accurate. The corrections for skewness make the results even more accurate for unequal sample sizes, such as case-control studies planned with a greater number of controls than cases.

Robert E. Tarone has been investigating statistical methods for sparse data situations such as those arising in the analysis of the distribution of mutations induced in a gene of known sequence and of the distribution of chromosome aberrations among bands in banded chromosome preparations. He has developed a multiple comparisons procedure which offers considerable improvement over standard methods for discrete, sparse data and has submitted a paper describing this procedure for publication. He is writing a second paper presenting methods developed to identify event "hot spots" in such discrete, sparse data situations.

Robert E. Tarone continues research on the theory of score tests and on methods for analyzing survival curves produced by in vitro exposure of cultured cells to DNA-damaging agents. He also continues research on methods for the statistical analysis of Gm immunoglobulin allotype data.

Hugh M. Pettigrew is continuing his research in the areas of synergism, risk assessment, and time-related factors in epidemiology. His interest in the mathematical theory of epidemics, the analysis of log-normal data, and tumor growth kinetics continues.

Jun-mo Nam has completed his research on comparison of Bernstein's and modified estimators of the recessive allele frequency in the HLA (human leukocyte antigen) system. The study showed that the modified method is more efficient and less biased than the standard Bernstein's method. A paper embodying the results has been submitted for publication.

Jun-mo Nam is investigating the development of efficient interval estimation of the coefficient of linkage disequilibrium between two particular alleles at different loci in the HLA system. He continues his research on efficient confidence intervals for the median effective dose (ED50) in quantal bioassay. Other continuing research efforts are statistical methods for comparing two or more harmonic trends in incidence and optimal allocation in strata matched case-control studies wherein cost per sample differs among the strata.

Robert E. Tarone and John J. Gart investigated the choice of statistics to evaluate the performance of cancer screening methods, deriving optimal statistics under certain models and comparing the efficiency of the various statistics. A paper reporting the results of their investigation has been accepted for publication.

John J. Gart and Jun-Mo Nam completed their research on confidence intervals for the absolute and relative differences of binomial proportions. The results are given in two papers, one recently published and the other accepted for publication. Related work is underway on the related problems of interval estimation of the attributable risk in stratified case-control studies and the determination of sample sizes in such studies. They are also studying the bias of the estimator of the common slope in stratified logistic models.

Donald G. Thomas has completely revised the program for "Trend and homogeneity analyses of proportions and life table data for use on a microcomputer." Originally developed for the mainframe with Gart and Breslow, this program analyzes data on several groups of observations in a single stratum. The original version continues to be frequently used at NCI and around the world in animal bioassay experiments where the groups consist of a control and several treated or exposed groups. In addition, the proportion analyses are used in epidemiological studies where the general case consists of time to tumor, relapse, or death with adjustment for censoring due to accidental death or loss to follow-up. Using data encoding and compression techniques, the new version can process, on a microcomputer, up to four times as many groups with much larger sample sizes than the original version. Although the input format is compatible with the original, the output format has been improved and the graphical capabilities enhanced. Care has been taken to ensure portability between most mainframes and micros.

Donald G. Thomas continues to improve the program for obtaining exact results in the analysis of combined 2 x 2 tables. The exact test for interaction may now be skipped for large data sets. An optional test for pooling tables has been added using methods developed by John J. Gart.

Alroy M. Smith provides computer support for several of these research efforts.

Publications:

Gart JJ. An application of score methodology: confidence intervals and tests of fit for one-hit curves. In: Rao CR, Chakraborty R. eds. Handbook of statistics Volume 8: Statistical methods for biological and medical sciences. Amsterdam: North-Holland (In Press).

Gart JJ, Nam J. Alternative confidence intervals for the relative difference. The statistician 1988;37:447-51.

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Tarone RE, Gart JJ. Significance tests for cancer screening trials. Biometrics (In Press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04269-18 BB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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.M. 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
5.0	5.0	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.)*

The Information Resources Management Section is responsible for providing computer-related support and services to all areas of the Epidemiology and Biostatistics Program. The 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.M. Stump	Chief, IRMS	BB	NCI
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

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 management, computer statistical analysis and information and reporting systems for a large program of epidemiological and biostatistical research. Overall coordination is provided for the management of various computer support services obtained under contract, for the procurement of other services obtained under contract, for the procurement of other Epidemiology and Biostatistics (E&B) Program research and resource contracts and for the acquisition and utilization of various information resources and automatic data processing equipment used by staff of the 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:

The Information Resources Management Section (IRMS) continues to execute a broad program of consultation and service in support of research projects having data management and statistical computing requirements. The primary focus of Section activities is directed toward support of Epidemiology and Biostatistics Program research; however, IRMS staff have routinely applied technical expertise to projects originating from various investigators throughout the NCI and NIH. In addition, resulting technologies, methodologies and data resources are shared with the extramural community.

The major recurring activities of the Section include contract procurement and administration, information management and dissemination as well as technical and consultative support to E&B Program investigators on research studies.

Major Findings:

This year the major challenge faced by the Section was maintaining the high quality of computer support and services provided to the Epidemiology and Biostatistics Program while containing their cost. The Section's comprehensive

approach to this problem included: 1) emphasizing use of personal computers as an adjunct to mainframe computing by means of conducting in-house seminars on relevant technical topics and administering a formalized program of PC support and assistance, 2) reviewing current computer use patterns and recommending alternative methods for more economical data management and statistical processing to address identified abusive and inefficient practices, 3) extending the use of computer facilities at the Frederick Cancer Research Facility as an alternative computing resource to the IBM mainframe at the NIH computer center, 4) maintaining a computer software inventory of widely used statistical and general purpose software and other data resources available for sharing within the Program, and 5) designing new monthly computer expenditure reports to more effectively manage computer-related budgets.

Individual staff members continued to provide support to new as well as on-going projects. Several noteworthy collaborations include: 1) updating population and mortality rate files with the latest available data from the Census Bureau and the National Center for Health Statistics, 2) extending the use and capabilities of a biospecimen inventory system that facilitates the management of biospecimen materials, and 3) reviewing alternative record linkage systems to evaluate their quality and cost effectiveness for cohort matching.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04475-12 BB

PERIOD COVERED

October 1, 1988 through September 30, 1989

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)* National Oceanic and Atmospheric Administration (G. Cotton, J. DeLuisi, L. Machta); EPA (H. Pitcher, J. Hoffman, J. Worrest); Temple U. (F. Urbach, D.Berger); U. Chicago (J. Frederick); George Wash. U.(F. Noonan, E DeEabo); United Nations Environmental Programme

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 physical measurements of solar ultraviolet radiation (UVB) and epidemiological data and analyses relevant to etiology of skin cancer, including malignant melanoma. Concerned that the "ozone hole" recently discovered above Antarctica may spread to populated regions of the world, an international agreement known as the Montreal Protocol was initiated which would restrict and eventually ban all man-made chlorofluorocarbons (CFCs), which are capable of reducing ozone in the stratosphere. Despite predications of long-term negative trends in ozone at very high altitudes, our surface-based measurements of solar radiation of 290 nm to 330 nm wavelengths (UVB) in the United States show no increasing trends, and continue to refute allegations that recent increases in the incidence of melanoma and skin cancer are directly related to ozone depletion. Increasing tropospheric ozone trends which may be related to heavy concentrations of UVB absorbing particulates, and perhaps increasing trends in cloud cover may explain these apparent (or temporary) discrepancies. We can now provide measurements of UVB in terms of minimal erythema dose (MED). For the average American Caucasian whose MED is 30 mJ/cm sq, the annual amount of UVB reaching the earth's surface varies from about 2,000 MEDS in northern locations to over 4,000 MEDS in southern locations, most of which are received during the months of May through August. Measurements of this type may be compared with those from other meters which simulate an erythema action spectrum. Trend analyses of skin melanoma rates indicate that increases in incidence vary by geographic location, age, sex, and anatomical site group. The greatest relative increase was observed for male trunk; decreasing trends were noted for youngest age (0-19).

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on the 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 health effects of harmful solar ultraviolet radiation (UVB, i.e., wavelengths between 290 nm and 320 nm). In particular (1) to provide measurements of solar ultraviolet exposure necessary to ascertain the human health effects of ultraviolet (UV) radiation resulting from anticipated ozone depletions in our biosphere; (2) to provide basic data to reduce the degree of uncertainity 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; (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/promoter 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 National Oceanic and Atmospheric Association Administration (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. The direct measurements obtained from ground level R-B meters are calibrated to count in terms of biological skin erythema, i.e., sunburn on a typical untanned, Caucasian skin. The minimal erythema dose (MED) is equivalent to approximately 30 mJ/cm^2. Time series analyses are employed to measure UV-B trends and compare with ozone measurements obtained from domestic and international sources. Also, air pollution measurements (e.g., SO_2 NOx, CO_2) from the Environmental Protection Agency are utilized to study trends of UV-B-absorbing particulates which may account for apparent discrepancies at specific urban sites. Monochromatic estimates of electromagnetic energy within the UV-B waveband which were derived from satellite data are also utilized. 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 skin cancer patients from registry files, and random

In assessing the relationship of UVB exposure and cutaneous malignancies, the new analyses with improved statistical methodology indicate that UVB remains the principal component after adjusting for certain host and environmental factors, such as skin and eye color, freckles, common moles or birthmarks, ethnicity, suntan ability, and outdoor occupations. However, the biological amplification factors (BAF), i.e., the relative changes in incidence which may be expected should UVB exposures increase by a certain percentage, may be a bit less than those which we provided from our earlier, unadjusted estimates. But the basic relationship between cell types remains unchanged; namely, that the effect of UVB on squamous cell carcinomas of the skin may be twice as great as that for basal cell carcinomas, and four times as great as that for skin melanomas. The BAFs were also found to be greatest for the exposed anatomical sites. The variances of the new estimates were substantially reduced, thus improving the reliability of the dose-response estimates.

Lifetime probabilities of developing skin cancer and skin melanoma were derived using survival data for specific geographic areas. After adjusting for deaths from other causes, Caucasians residing in the southern regions of our country are at greater risk than their counterparts in northern regions, by a factor of about two.

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 than 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 principal occupation. Attributable risk (AR) estimates were calculated to measure the impact of these factors on the population risk for skin cancer. AR's 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 were found to be increasing at annual rates of 3 and 6 percent, respectively. Based on these rates cases would double within the next 15 years. However, during the early 1980s skin melanoma incidence rates leveled off, with decreases observed among Caucasian women. This trend did not persist as surveillance and reporting procedures had apparently changed in certain SEER areas during 1984 and 1985, resulting in the highest overall incidence rate for 1985 that has ever been reported in the U.S. Time series methods will be utilized to account for recent short-term interventions in making projections for skin melanoma incidence and mortality by specific geographic area.

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:

The amount of solar ultraviolet UV-B wavelengths of 290 to 320 nm reading the earth's surface has not increased at eight geographic locations in the United States from 1974 to 1985, a period of about one solar cycle. Overall, an average annual decrease of about 0.7 percent was observed, with 3 of 8 locations showing no statistically significant trends. Similar patterns were noted for 6 other U.S. locations where UVB monitors were in operation for shorter time periods.

Increasing amounts of tropospheric ozone and urban air pollution are suspected as contributing factors which may account for decreasing UVB trends. However, at Manuna Loa, a remote, sparsely populated location situated at 3.4 km above sea level, UV did not increase during the 1980s, in contrast to stratospheric ozone decreases reported during similar time spans. Our research has prompted investigations of the influence of UVB-absorbing particulates in the atmosphere.

Our findings further suggest that lifestyle patterns of sunlight exposure, and not stratospheric ozone depletions, may be primarily responsible for recent increases in skin cancer incidence, including melanoma. It is expected, however, that future ozone depletions, which are projected to increase throughout the 21st century, will result in excess risks for skin cancer and other diseases if preventive measures are ignored.

Except for the beneficial photobiologic effects of UVB exposure on the development of vitamin D through the skin, excess amounts of UVB reaching the earth's surface will change our ecology and do much harm to life on our planet. Recent concerns have also focused on the negative correlations of breast cancer and colon cancer mortality rates with sunlight exposure and a deficiency of dietary vitamin D among older men and women. Current studies will explore the UV hypotheses for other diseases not seriously considered by most researchers in the past.

Preliminary analyses of data from a pilot study obtained from collaborators at George Washington University indicate that a photosensitive, natural element found in human skin may be involved in the immunosuppression process through the Langerhans' cells. Adequate photochemical epidemiologic studies are required to substantiate early impressions and findings with respect to skin cancer risk among specific population groups.

Publications:

Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 1987;123:241-50.

Leong GKP, Stone JL, Farmer ER, Scotto J, Reizner GT, Burnett T, Elpern DJ. Nonmelanoma skin cancer in Japanese residents of Kauai, Hawaii. J Am Acad Dermatol (In Press).

Scotto J, Fears TR. The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States. Cancer Invest (In Press)

Scotto J, Cotton G, Urbach F, Berger D, Fears T. Biologically effective ultraviolet radiation:surface measurements in the United States, 1974 to 1985. Science 1988;239:762-4.

Scotto J, Cotton G, Urbach F, Berger D, Fears TR: Global stratospheric ozone and UVB radiation. Science 1988;242:1111-2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04500-12 BB

PERIOD COVERED: October 1, 1988 to September 30, 1989

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	Head, Epidemiologic Methods Section	BB	NCI
Others:	W.J. Blot	Chief	BB	NCI
	P.F. Dahm	Visiting Statistician	BB	NCI
	T.R. Fears	Mathematical Statistician	BB	NCI
	J.H. Lubin	Health Statistician	BB	NCI
	J.K. McLaughlin	Epidemiologist	BB	NCI
	P.S. Rosenberg	Staff Fellow	BB	NCI
	S. Wacholder	Senior Staff Fellow	BB	NCI

COOPERATING UNITS (if any)
Mayo Clinic (S. Wieand), Univ. of Paris (J. Benichou), Chinese Acad. of Med. Sci. (Y. Liu), McGill Univ. (J.F. Boivin, J. Siemiatycki), Johns Hopkins Univ. (R. Brookmeyer, S. Piantadosi), NIEHS (C. Weinberg)

LAB/BRANCH
Biostatistics Branch

SECTION
Epidemiologic Methods Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.3	3.1	0.2

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 paper is in press on new methods for analyzing case-control studies in which controls are obtained by cluster sampling, and weighted sampling schemes for case-control studies and methods for efficiently allocating control sampling among strata with variable costs of control sampling were developed. Variance calculations and methods for estimating the efficiency of the case-cohort design, compared to other methods for sampling large cohorts were determined. Research on efficient methods for analyzing data in which exposures are measured with error and for evaluating the usefulness of supplemental error-prone data is in progress, and a volume from a workshop on errors in variables. is in press. Empirical studies indicated that only rarely will estimated risks from occupational exposures be seriously distorted by failure to control for smoking history, which is often unavailable. Complex relative risk models were used to analyze the risks from exposure to radon in the United States. It was estimated that removal of exposures above the EPA's ''action level'' could save nearly 4,000 deaths annually. Staff developed methods of inference for estimates of the attributable risk obtained from a logistic model for case-control data. Work on goodness-of-fit for the logistic model was also published. Work on the statistical method of ''backcalculation'' for projecting AIDS incidence and for estimating previous trends in infection was published, and new methods have been developed to speed these calculations and to evaluate the uncertainties in these projections systematically. A paper was also published that compared the effectiveness and numbers of tests required for various programs of voluntary confidential testing for human immunodeficiency viruses. A system of computer programs for epidemiologic analyses on the IBM-PC is nearly ready for distribution. A paper was also written on how to adapt the PHGLM Procedures in SAS for specialized types of survival analyses.

Project Description

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

M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
W.J. Blot	Chief	BB	NCI
P.F. Dahm	Visiting Statistician	BB	NCI
T.R. Fears	Mathematical Statistician	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
P.S. Rosenberg	Senior Staff Fellow	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
J.K. McLaughlin	Epidemiologist	BB	NCI
J.D. Boice	Chief	REB	NCI
L.A. Brinton	Chief, Environmental Studies Section	EEB	NCI
D.P. Byar	Chief, Biometry Branch	DCPC	NCI
S.B. Green	Medical Researcher	DCPC	NCI
P. Hartge	Epidemiologist	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
J.J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI
J. Nam	Mathematical Statistician	BB	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 and Biostatistics Program, and elsewhere.

Major Findings:

Work continues on methods for selecting controls and other aspects of the design and analysis of case-control studies. A paper (in press), written in collaboration with Dr. B. Graubard of the National Institute for Child Health and Human Development (NICHD), describes the effects of cluster sampling of controls on standard methods of case-control analysis and proposes correct analytical procedures for this design. Such cluster samples could arise, for example, in telephone surveys of controls. In collaboration with Dr. C. Weinberg of the National Institute of Environmental Health Sciences (NIEHS), Branch staff have submitted a manuscript on weighted case-control sampling in which the

probability of selection for a detailed interview depends both on case-control status and on the level of some easily determined covariate, such as whether or not the subject is currently smoking. Two Branch members are studying efficient allocation of controls among strata for a case-control study in which the costs of finding and interviewing controls varies among strata.

Several staff members have been working on the development of efficient designs and methods of analysis for large cohorts. A paper was published that described a new method of analysis for the case-cohort design and calculations to compare the efficiency of that design with nested case-control sampling. Another paper illustrates the usefulness of the case-cohort design to detect risk factors for second cancers. A third paper is in preparation that generalizes the class of designs for sampling a large cohort and that describes how to compare the efficiencies of various methods of sampling exposure information from a large assembled cohort. Work is also in progress to adapt the methods of Poisson regression to data from case-cohort studies.

A special volume summarizing the results of a workshop on designing and analyzing epidemiological studies in which exposures are measured with error is in press. This volume was edited by Branch staff and staff at the Division of Cancer Cause and Prevention. One Branch member is completing research to compare the efficiencies of available methods of analyzing error-prone data from cohort and case-control studies with dichotomous exposures and responses and to determine how much information can be gained by taking additional error-prone measurements to supplement an initial set of data that includes both error-prone and ''gold-standard'' exposure measurements.

One paper, written in collaboration with Professor J. Siemiatycki of McGill University, has appeared and provides empirical evidence that reliable inference on occupational exposures is often obtained even in the absence of data on potential confounders including smoking status and socioeconomic status. Biostatistics Branch staff and members of the Environmental Epidemiology Branch have reviewed occupational and smoking histories from 3,627 white men and 1,200 white women selected randomly from ten areas of the United States in 1977-1978. Calculations based on Axelson's method indicate that unmeasured smoking patterns will only rarely distort relative risks from occupational studies by more than 30%. A manuscript has been submitted on these findings.

Branch staff have written several papers on the evaluation of risk in epidemiologic studies. One paper has appeared and two others are in press on cancer risks from exposure to radon. Complex relative risk models were required to take the temporal pattern of exposure into account. These papers also discuss the effects of variable selection in forming risk models and the effects of errors in exposure assessment. As much as 10% of all lung cancers in the U.S. may be attributable to radon exposure. Under the assumption that the model developed by the National Academy of Science's Committee on the Biological Effects of Ionizing Radiation (BEIR IV), which was based on data from underground miners, holds broadly for exposures to household radon, it is estimated that 3,800 lives can be saved annually by eliminating exposures above the EPA's ''action level'' of 4 picoCuries per liter.

In collaboration with Dr. J. Benichou of the University of Paris, statistical methods have been devised to put confidence limits on estimates of attributable risk calculated from case-control data using a logistic risk model. A paper on this topic has been submitted, and a preliminary paper outlining the underlying statistical theory for implicit functions has appeared. A related manuscript on statistical inference for estimates of absolute risk from cohort studies has also been submitted. These methods have been tested and implemented in a manuscript on projecting the chance of developing breast cancer for a woman of a specific age with specific breast cancer risk factors. In collaboration with Professor R. Makuch of Yale University, a Branch member published a paper on goodness-of-fit of the logistic risk model.

Joint work with Professor R. Brookmeyer of Johns Hopkins University was published describing the method of ''backcalculation'' for projecting the size of the AIDS epidemic. Branch staff have recently developed very rapid regression methods for performing backcalculation. Using these methods, Branch staff are evaluating the systematic and random uncertainties of projections of AIDS incidence and estimates of trends in previous infection rates derived by backcalculation. A paper evaluating the potential benefits of voluntary confidential HIV testing in a mixed population of homosexuals, bisexuals and heterosexuals indicated that emphasizing the testing efforts on the homosexual and bisexual subgroups prevented more disease and required fewer tests than testing the entire population uniformly. This paper represented the joint efforts of Branch staff and of Dr. D. Preston of the Radiation Epidemiology Branch and Professor S. Piantadosi of Johns Hopkins University.

A paper appeared which indicates that it is preferable not to include a ''don't know'' option for many questionnaire items. Removing this option was shown to reduce the amount of missing data without decreasing the reliability of the response.

A paper with S. Wieand of the Mayo Clinic on the comparison of diagnostic tests was revised and accepted for publication.

One Branch member continues to collaborate with members of the Radiation Epidemiology Branch to develop an extensive set of programs for epidemiologic analysis with the IBM-PC. These programs include many special features, including methods for open cohorts, time-dependent covariates, complex models for the relative hazard, and variance calculations for case-cohort data. Branch staff also wrote a paper (in press) on how to adapt the PHGLM Procedure in SAS for analysis of time-dependent covariates and case-cohort data.

Publications:

Benichou J, Gail MH. A ''Delta Method'' for implicitly defined random variables. Am Stat 1989;43:41-4.

Boivin JF, Wacholder S. Determination of risk of second cancers in patients treated for a first cancer. Revue Epidém Santé Publ 1988;36:292-300.

Brookmeyer R, Gail MH. A method for obtaining short term projections and lower bounds on the size of the AIDS epidemic. J Am Stat Assoc 1988;83:301-8.

Byar DP, Gail MH. Workshop on errors-in-variables. Stat Med (In Press).

Gail MH. Comments on ''Interim analyses: the repeated confidence intervals approach'' by C Jennison and BW Turnbull. J R Stat Soc B (In Press).

Gail MH. Review of ''Statistical Methods in Cancer Research, vol II. The Design and Analysis of Cohort Studies,'' by NE Breslow and NE Day. Stat Med (In Press).

Gail MH, Brookmeyer R. Methods for projecting course of acquired immunodeficiency syndrome epidemic. JNCI 1988;80:900-11.

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Graubard BI, Fears TR, Gail MH. Effects of cluster sampling on epidemiologic analysis in population based case-control studies. Biometrics (In Press).

Lubin JH. Models for the analysis of radon exposed populations. Yale J Biol Med 1988;61:195-214.

Lubin JH. On the BEIR IV lung cancer risk projection model for radon exposure. In: Proceedings of the 24th annual meeting of the National Council on Radiation Protection and Measurements. Bethesda, MD: National Council on Radiation Protection and Measurements (In Press).

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Makuch RW, Rosenberg PS. Goodman and Kruskal's Lambda: a new look at an old measure of association. Stat Med (In Press).

McLaughlin J, Brookmeyer R. The epidemiologic approach. In: McCunney RJ, ed. Handbook of occupational medicine. Boston: Little Brown and Co, 1988;282-96.

Pee D, Wacholder S. The PHGLM procedure for time-dependent covariates and the case-cohort design. In: Proceedings of the fourteenth annual SUGI conference. Cary, N.C.: SAS Institute, Inc. (In Press).

Poe GS, Seeman I, McLaughlin JK, Mehl ES, Dietz M. Effects on level and quality of response of the inclusion of "don't know" boxes in factual questions in mail questionnaires. Pub Opin Quar 1988;52:212-22.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01CP04779-13 BB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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.J. Blot	Chief	BB	NCI
Others:	J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
	R.H. Hoover	Chief	EEB	NCI
	B.J. Stone	Mathematician	EEB	NCI

COOPERATING UNITS *(if any)* Med. Univ. SC (S. Schuman); NJ Dpt. Health (J Schoenberg); Chinese Acad. Med. Sci. (B. Li); Shanghai Cancer Inst (Y Gao); Beijing Inst. Cancer Res. (W. You) Center Prev Med. (E. Buiatti); Univ. So. Ca. (S. Preston-Martin); Emory Univ. (R. Greenberg); Ca. Hlth. Dpt. (D. Austin)

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 analyses of data from case-control studies of esophageal cancer in coastal South Carolina and of oral cancer in Atlanta, New Jersey, Los Angeles, and San Francisco. 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. In the four-center study, smoking and drinking tended to combine in a multiplicative fashion to enhance oral cancer, with heavy consumers experiencing more than 35 times the risk of abstainers. 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. Smoking was shown to be the dominant cause of lung cancer among men in Shanghai, while exposures to cooking oil volatiles were implicated in the high risk of lung adenocarcinoma among women, most of whom were nonsmokers. Consumption of fermented pancakes, a preference for salty food, and smoking were related to the high risk of stomach cancer in Shandong, China, while protective effects were found for vegetable intake, including garlic. A case-control study of gastric cancer in areas of Italy that have among the world's highest rates of this malignancy revealed elevated risks associated with intake of preserved meats, while protective effects were found for fresh fruit, vegetable and garlic consumption.

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.H. Hoover	Chief	EEB	NCI
B.J. Stone	Mathematician	BB	NCI
L.A. Brinton	Chief, Environmental Studies Section	BB	NCI
L.M. Pottern	Epidemiologist	BB	NCI
L.M. Brown	Epidemiologist	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
R.G. Ziegler	Cancer Expert	EEB	NCI
M.S. Linet	Cancer Expert	EEB	NCI
R.G. Hayes	Cancer Expert	EEB	NCI
A.G. Ershow	Senior Staff Fellow	BB	NCI
J.K. McLaughlin	Epidemiologist	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
M.H. Schiffman	Medical Staff Fellow	EEB	NCI
D.T. Silverman	Epidemiologist	BB	NCI
P. Greenwald	Director	DCPC	NCI
P.R. Taylor	Epidemiologist	DCPC	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:

Collaborative case-control and cohort studies in the United States: The Branch undertakes collaborative analytical investigations to identify and quantify risk factors for cancer. In the largest investigation of oral and pharyngeal cancer yet conducted, staff have worked with scientists in Atlanta, New Jersey, Los Angeles, and the San Francisco area in the design and conduct of a population-based case-control study. Published during the year were results of analyses of interview data from nearly 1,200 cancer patients and 1,300 controls, which showed smoking and drinking to be the dominant risk factors. The large study size enabled the first clear demonstration of effects of alcohol consumption among lifelong nonsmokers and indicated that smoking and drinking tended to combine more in a multiplicative than additive fashion in affecting oral cancer risk. Risks of oral/pharyngeal cancer were shown to fall sharply following cessation of smoking. Smokeless tobacco was also implicated as a risk factor among nonsmokers, although the numbers of users were too small for detailed analyses of the relative influences of snuff vs. chewing tobacco. Dietary analyses of oral cancer risk showed significantly protective effects associated with high fruit intake, with those in the highest quartile of consumption at less than half the risk of those in the lowest.

Tobacco and alcohol were also found to be the principal determinants of esophageal cancer in coastal South Carolina, where rates of this tumor have long been elevated among blacks. Results published during the year from this case-control study conducted with the Medical University of South Carolina revealed that consumption of local moonshine whiskies, reported by nearly 90% of the black male patients interviewed, appears to be responsible, at least in part, for the clustering. Higher risks were independently associated with poor nutrition, providing further evidence of a dietary component in the etiology of esophageal cancer and additional clues to its higher rates among blacks than whites. Interviewing continued during the year for another case-control investigation of esophageal cancer. Nearly 600 patients and more than twice as many population-based controls in Atlanta, Detroit, and New York will be enrolled in this collaborative study focusing on differences in exposures and risks between blacks and whites. Utilizing the same control series for comparison, patients with cancer of the pancreas and multiple myeloma are also being enrolled. Each of these cancers occurs more frequently in blacks than whites for as yet unknown reasons.

Data analyses continued on two large population-based case-control studies: the national bladder and skin cancer surveys which included areas at high as well as low risk of these cancers. Both surveys were conducted in the late 1970s, but provide data from nearly 19,000 interviews on population exposures and risk factors for these tumors that are still applicable today. The contribution of occupational exposurers to bladder cancer risk was explored during the year, with best estimates of the attributable risk of "high-risk occupations" placed at about 20% among males and about 5% among females. The relative risks of occupational bladder cancer were similar in men and women, although the rate of exposure to occupational carcinogens was substantially lower in women. Occupational bladder cancer among nonwhite men was similar to that among white men. There was, however, some evidence of risk differences between whites and nonwhites that appeared to be due to racial differences in exposure among men within the same industry and job title. These data also provide for the most

definitive evaluation of the relation of cigarette smoking to bladder cancer risk. Clear trends were observed with duration and intensity of smoking, with detection, for the first time, of a rapid reduction in risk within a few years of quitting smoking. This pattern was seen both in the U.S. and in Italy, where case-control data also showed markedly higher bladder cancer risk associated with smoking black compared to blond tobaccos. The increased carcinogenic potential of the black tobacco is further suggested by the detection of hemoglobin adducts to 4-aminobiphenyl (a bladder carcinogen) in the blood of smokers of black tobacco.

Field work neared completion in case-control studies of biliary tract cancer in collaboration with the University of Southern California (USC) and renal pelvis cancer in collaboration with USC, the New Jersey Department of Health, and the University of Iowa. The latter investigation was prompted by an earlier Branch study in Minnesota, which revealed an association between renal pelvis cancer and long-term use of acetaminophen-containing analgesics. The finding was based on small numbers of observations, but is of concern because of a recent report of carcinogenicity in an animal experiment with this commonly used medication. Data from the Minnesota study published this year showed that use of diuretics was associated with increased renal adenocarcinoma risk, consistent with a similar finding from Los Angeles published last year. The biliary cancer study is one of the few etiologic investigations of this relatively rare tumor.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that 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 have been conducted in these investigations.

In Shanghai smoking was shown to be 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 were nonsmokers, however, so other factors account for their high rates. What these factors are remain to be clarified, but a clue arises from the observations of increased risk among women reporting greater frequencies of high temperature wok cooking, increased house smokiness and eye irritation when cooking, and greater use of rapeseed cooking oils. The link to rapeseed oil is intriguing since rapeseed volatiles have been reported to be mutagenic in the Ames test. Initial results from analyses at NCI's Laboratory of Human Carcinogenesis confirm reports from China of mutagenic activity of rapeseed oil volatiles, with further characterization of the oils now underway. Occupational analyses revealed a lowered risk of lung cancer among workers in the cotton textile industry, a major employer in Shanghai. The finding is consistent

with reports from the U.S., and raises the possibility of exposure to protective agents (e.g., endotoxins) in the work environment.

In Shenyang, cigarette smoking also was a strong risk factor, with a higher prevalence of smoking among females compared to elsewhere in China contributing to the area's high rates. Air pollution was also a significant factor, with risk rising in proportion to exposure to indoor pollutants from coal-burning Kang and other home heating devices. Occupational determinants were also found, with a 3-fold increased risk of lung cancer among workers in one of China's largest copper smelters and among males living within 1 km of the smelter's central stacks.

In Shandong, dietary differences distinguished cases and controls. The stomach cancer patients preferred and consumed more salted foods and more of the local favorite sour pancakes, and significantly less fresh vegetables. The most marked protective effects were for vegetables of the allium class, including garlic, of note because of the tumor-inhibitory properties of allium reported from experimental studies. To follow up on these leads and evaluate whether diet similarly affects the origins of precancerous lesions (chronic atrophic gastritis, dysplasia) of the stomach, additional research was launched during the year in Shandong. Three thousand adults in this high-risk area are being enrolled in a screening program to detect early cancers and contrast questionnaire and biochemical markers between those with various precursor lesions. They will then be followed to directly evaluate rates of transition to more advanced states, including gastric cancer.

In the Linxian case-control study, consumption during adulthood of pickled vegetables was not found to be the strong risk factor it was suspected to be. Intake of pickled vegetables in either the 1950s or 1970s was not higher among the esophageal cancer patients, nor was intake of fresh fruit and vegetables lower. Instead the cases were characterized by lower fluid and higher wheat and corn intake, similar to Iran where clusters of high esophageal cancer rates have also been found.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,400 persons with esophageal dysplasia. 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 a one-half replicate of a 2^4 factorial design, is used for the general population trial. A brief questionnaire was administered and 5 ml serum obtained from each participant prior to enrollment. The studies, now in their fourth and third years, respectively, 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. Assays of nitrosamines in urine specimens collected from trial participants are planned to assess whether N-nitroso compounds may be involved in the carcinogenic process. Increases in cell proliferation, based on tritiated thymidine labelling assays performed at the Memorial Sloan-Kettering Cancer Center, were found among Linxian residents with histologic evidence of dysplasia.

Additional collaborative research in China was conducted during the year, including cohort studies evaluating the cancer experience of occupational groups exposed to benzene, silica, radon and arsenic. The benzene study is enrolling 100,000 workers to enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. During the year benzene air level measurement and other exposure data since 1949 or thereafter were collected from 700 factories in 12 cities. Cohort follow-up has begun, and plans for a nested case-control study of leukemia developed. The silica study will assemble 10,000 persons in central China with silicosis, plus 50,000 persons heavily exposed to silica without silicosis, for evaluation of this agent that has been recently shown to initiate and promote cancer in experimental animals. The radon/arsenic study focuses on nearly 30,000 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.

A case-control study of stomach cancer, in collaboration with the Center for the Study of Cancer in Florence and other Italian institutions, was conducted to investigate reasons for the high risk of this cancer in north and central parts of Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Analyses of interview data from 1,000 cancer patients and 1,100 controls, completed during the year, revealed strong dietary associations. Increased risks were associated with certain traditional soups and preserved meats, while decreased risks were linked to intake of fresh fruits and vegetables. Protective effects were also associated with garlic consumption.

Plans were also formulated this year for the conduct of a case-control study of renal cancer in Sweden, Denmark, Germany, Australia, Shanghai and the United States. Rates of this cancer in Scandinavia are among the highest in the world.

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You WC, Blot WJ, Chang YS, Ershow A, Yang ZT, An Q, Henderson BE, Fraumeni JF Jr. Jr. Wang TG. Allium vegetables and reduced risk of stomach cancer. JNCI 1989;81: 162-4.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05498-04 BB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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	Head, Epidemiologic Methods Section	BB NCI
Others:	T.R. Fears	Mathematical Statistician	BB NCI
	P.F. Dahm	Visiting Statistician	BB NCI
	J.H. Lubin	Health Statistician	BB NCI
	P.S. Rosenberg	Staff Fellow	BB NCI
	S. Wacholder	Senior Staff Fellow	BB NCI

COOPERATING UNITS *(if any)* Hemophiliac Study Group; Mothers and Infants Cohort Study Group, Univ. of California at Los Angeles (R. Elashoff); Cancer Inst. of the Chinese Academy of Med. Sciences (J.Y. Li); McGill Univ. (J. Siemiatycki); Veterans Administration Clinical Trials Program

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.6	0.2

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) Analysis of joint risk of lung cancer from exposure to radon, arsenic and tobacco products; (2) data acquisition from large scale case-control and cohort studies in Gejiu City, China to further quantitate these relationships; (3) analysis of data on risk of thyroid; cancer following exposure to radiation of the head and neck; (4) evaluation of case-control data on dietary risk factors for esophageal cancer; (5) evaluation of fecal mutagens; (6) studies of the effects of treatment for childhood cancer on subsequent rates of menopause and on patterns of marriage and divorce; (7) application of the method of backcalculation for projecting AIDS incidence and for estimating previous trends in infection for various subgroups of the population; (8) assisting members of the Viral Epidemiology Section on the design and analysis of studies of natural history, transmission rates, and biological markers in cohorts of hemophiliacs and infants exposed to HIV; (9) evaluating DNA fingerprints as an aid to quality control in tissue culture laboratories; (10) monitoring clinical trials of nutritional supplements to prevent cancer, of interventions to reduce smoking, and of therapies to prevent AIDS among infected groups; (11) providing consultation on the use of newly developed computing packages for epidemiologic analysis, and providing consultation on statistical methods to analyze error-prone exposures.

Project Description

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

M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
T.R. Fears	Mathematical Statistician	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
P.F. Dahm	Visiting Statistician	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
P.S. Rosenberg	Staff Fellow	BB	NCI
D.P. Byar	Chief, Biometry Branch	DCPC	NCI
J.J. Goedert	Cancer Expert	EEB	NCI
W.A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
A. Krämer	Special Volunteer	EEB	NCI
J.M. Byrne	Visiting Associate	CEB	NCI
J.D. Boice	Chief	REB	NCI
E. Ron	Senior Staff Fellow	REB	NCI
C.E. Land	Health Statistician	REB	NCI
L.A. Brinton	Chief, Environmental Studies Section	EEB	NCI

Objectives:

To promote the use of sound methodology in a wide range of observational and experimental studies by collaboration or consultation 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 has completed two manuscripts (in press) in collaboration with members of the Cancer Institute of the Chinese Academy of Sciences on joint risks of lung cancer from exposure to radon, arsenic and tobacco products. In this investigation of tin miners in China's Yunnan Province, excess risks were found among underground miners heavily exposed to radon. About half the unadjusted risk from radon could be accounted for by exposures to arsenic and tobacco products, which were also significant risk factors in this population. Additional data collection for large-scale case-control and cohort studies among tin miners in Gejiu City, China is nearing completion to quantitate the joint effects of smoking and exposure to radon and arsenic on risk for lung cancer.

Dr. Lubin is participating in a collaborative analysis with members of the Radiation Epidemiology Branch and extramural researchers to reassess long-term thyroid cancer risk in six cohorts of individuals exposed to radiation of the head and neck. Dosimetry is now complete and analyses are underway to evaluate

the effects of sex, age at irradiation, ethnicity, dose, and, if possible, dose fractionation on risk of cancer in these cohorts.

Dr. Wacholder has collaborated with other members of the Biostatistics Branch on an analysis of risk factors for esophageal cancer in Linxian, China (in press). The case-control data in this study do not indicate an association with ingestion of pickled vegetables, as had been conjectured (see also Z01CP04779-13 BB).

Dr. Wacholder collaborated with Dr. Schiffman of the Environmental Studies Section on a study of mutagenicity and fecapentaene concentration in stool samples. The work suggests that other mutagenic factors may be important in addition to fecapentaenes. Although fecapentaene concentration explained much of the mutagenicity measured by the Salmonella TA100 strain, it did not explain mutagenicity measured by the TA98 strain.

Drs. Fears and Gail are collaborating with Dr. Byrne of NCI's Clinical Epidemiology Branch to quantify the effects of childhood treatment for cancer on early menopause among 1,112 survivors of childhood cancer and among 1,648 matched controls. Most of the data pertain to children treated between the ages of 13 and 19. Among such subjects who are menstruating at age 21, rate of subsequent menopause is accelerated in those treated with radiation, and especially in those who were given radiation below the diaphragm together with alkylating agents. Those treated surgically had menopausal rates comparable to controls. Additional work by Dr. Fears and members of the Clinical Epidemiology Branch demonstrates that survivors of childhood cancer have marriage and divorce rates similar to controls except for survivors of brain tumors, who were less likely to marry, and for male survivors of brain tumors and retinoblastomas, who were prone to divorce.

Two of Dr. Fears' papers with Professor Robert Elashoff of UCLA and with Dr. Marvin Schneiderman (National Academy of Sciences) appeared describing the interactive effects of joint exposures to carcinogens in rodent assays. This work used tests for interaction that were recently developed for survival data. Although in most cases no antagonistic or synergistic effects were found, it was discovered that nitrilotriacetic acid reduced the carcinogenic potential of N-methyl-N'-nitrosoguanidine for stomach cancer and of N-butanol-N-butylnitrosamine for bladder cancer.

Dr. Fears also collaborated with Mr. Scotto of NCI's Biostatistics Branch to describe the reliability of measurements of solar ultraviolet radiation obtained from urban monitoring sites. It was concluded that measurements at urban sites were valid despite the fact that local pollution may alter the amount of radiation reaching these sites.

Drs. Gail and Rosenberg are supporting efforts of the Family Studies Section to study the natural history of AIDS. Dr. Gail is collaborating in a cohort study of mothers and infants at risk of developing AIDS. A manuscript has been written indicating that exposure to HIV in utero has no significant effects on measurements made at birth, such as Apgar score and birth weight. Drs. Gail and Rosenberg are collaborating in a study of a cohort of hemophiliacs, whose dates of seroconversion may be determined from stored sera. A manuscript on the

prognostic significance of p24 antigen and T4 markers in this cohort is now in press. Drs. Rosenberg and Gail have outlined analyses for studies of rates of transmission from HIV infected hemophiliacs to their wives. Dr. Gail, in collaboration with Dr. Krämer of the Viral Epidemiology Section, has written a paper on the prognostic significance of neopterin as a marker for progression to AIDS. Dr. Rosenberg is leading the effort to apply the technique of backcalculation for projecting future AIDS incidence and estimating previous trends in HIV infection for subgroups defined by risk behavior, geography and race. Dr. Gail serves as Chairman of the Operations Committee that monitors the progress of a placebo-controlled clinical trial of azidothymidine, sponsored by the Veterans Administration, among patients with AIDS-related complex, and he has recently been asked to assist in the protocol design for a VA-sponsored vaccine trial against HIV.

Dr. Gail is collaborating with Drs. Gilbert and O'Brien of DCE's Laboratory of Viral Carcinogenesis to assess the usefulness of DNA fingerprints for detecting contamination in tissue culture cell lines.

Dr. Gail and collaborators in the Environmental Studies Section, the Clinical Epidemiology Branch and DCPC have completed a manuscript describing methods to project individualized breast cancer risk over fixed time intervals for women of a given age with specific risk factors. Projected risks range from low values to up to over 50%, depending on the duration of follow-up and the presenting combination of risk factors, which include early menarche, delayed first live birth, previous breast biopsies, and an adverse family history.

Dr. Gail collaborated with members of the Division of Cancer Prevention and Control on the design of a large-scale randomized study of interventions to reduce smoking. Eleven matched pairs of cities were selected, and one member of each pair has been randomly allocated to active intervention while the other city serves as control.

Dr. Gail is collaborating with Dr. Blot and with members of DCPC to monitor a large-scale randomized trial to determine whether vitamin supplements can reduce gastric and esophageal cancer incidence. The trial will run for another 2 years before the treatment codes are unblinded and treatment comparisons revealed (see also Z01CP04779-13 BB).

Staff members also provided numerous consultations on statistical methodology and computer methods during the year. In particular, Dr. Lubin has given several presentations and numerous consultations to assist members of the Program in the use of a powerful set of computer programs for epidemiology called EPITOME. Professor Dahm has consulted with several members of the Occupational Studies Section and Environmental Studies Section on statistical methods of analysis for data in which exposures are measured with large error or uncertainty.

Publications:

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ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

The Branch plans and conducts independent and collaborative studies on the distribution and determinants of human cancer, with special emphasis on host factors as detected by clinical observations, and on epidemiologic and laboratory research for clues to carcinogenic mechanisms. Other studies concern cancer in relation to exposures to ionizing radiation or certain viruses; the health and reproductive performance of persons who were treated successfully for childhood cancer; the use of national mortality data developed within the Branch to describe geographic and other demographic features or to test hypothesis about cancer deaths; the development of new epidemiologic resources; and the provision of overviews, consultations and advice, when requested, at the local, national and international level.

Highlights of the Last Year:

- In our families with the Li-Fraumeni family cancer syndrome (sarcomas, breast cancer and other neoplasms), the gene for the disorder has apparently been located close to the gene for retinoblastoma.

- In our families with the nevoid basal cell carcinoma syndrome, the gene locus is suspected to be on chromosome 1 or 15.

- In an unusual multi-case Wilms' tumor family, there was no evidence for the gene on chromosome 11 as in other forms of the neoplasm.

- Rubinstein-Taybi syndrome (broad thumbs, abnormal facies and mental retardation) was found to have a high frequency of spontaneous keloids, as well as trauma-induced keloids, and possibly tumors due to developmental errors.

- In an international collaborative effort to follow-up the prior assignment of the gene for neurofibromatosis 1 to chromosome 17, we contributed to and helped compile data on 13,800 genotypings for 31 DNA markers in 142 families with 700 affected persons. Multipoint analysis identified two flanking markers, pHHH 202 and EW206, which had 95 percent upper confidence limits of 4 and 9 cM, respectively, from the disease gene locus, as close as markers now in clinical use for cystic fibrosis.

- The first confirmatory report was made of the assignment of the gene for multiple endocrine neoplasia type 1 to chromosome 11, with demonstration of its linkage to the gene INT2.

- In an effort to make assays of sister chromatid exchanges feasible for use by genetic epidemiologists, the phenomenon was compared in whole blood, separated fresh lymphocytes, and cryopreserved lymphocytes with and without in vitro exposure to known mutagens. Predictable, systematic differences in response were documented.

- The Interinstitute Medical Genetics Program continued to provide a clinical resource for the Branch and NCI colleagues, to train Fellows and medical students in clinical genetics, and to expand genetic research among the intramural research units of the NIH.

- Our five-registry study of the late effects of cancer and its therapy on the health of long-term survivors of childhood and adolescent cancer involved interviewing 2,283 survivors and 3,270 of their siblings as controls about their health, their reproductive experiences and the health of their children. This year's results include:

  A substantial proportion (14%) of survivors of non-central nervous system (CNS) tumors did not know that they had cancer; these survivors were more likely to be non-white, to have been diagnosed in earlier years, and to have come from Connecticut.

  Marriage was less likely in survivors by about 14 percent; however, the marriage deficit was more pronounced in males than females, and was substantial only in CNS tumor survivors.

  Although divorce rates overall were unchanged in survivors compared to controls, men who had survived CNS tumors diagnosed before they were 10 and men who had been treated for retinoblastoma were more likely to have their first marriages end during the follow-up period.

  Pregnancies in female survivors of Wilms' tumor were about four times more likely to end adversely than pregnancies in controls. Furthermore, these women seemed more likely to have a congenital defect of the reproductive tract.

  Both this study and another by our group in Boston showed low birth weight and other adverse outcomes of pregnancies of mothers, but not fathers, who had received radiotherapy for Wilms tumor.

- End-stage renal disease with dialysis was linked to an excess of renal cell carcinoma in non-whites, but not in whites.

- A study of thyroid nodules was conducted among older women in an area of high background radiation in China. No excess was found in a collaborative study by Dr. Boice of the Radiation Epidemiology Branch, Dr. Beebe, and others.

- A Branch-generated study of the skin fibroblast sensitivity in vitro was made of women with breast cancer vs. other women, atomic-bomb exposed vs. non-exposed. The study, made in collaboration with the staff at the Radiation Effects Research Foundation, showed no difference with respect to cell-killing by acute radiation exposure.

- Experimentation with mapping U.S. cancer mortality by economic subareas that cross state lines revealed some hot-spots not apparent by use of the traditional State Economic Areas (which do not cross state boundaries).

OFFICE OF THE CHIEF

Clinical Epidemiology

Renal cell carcinoma after dialysis: In Japan, 119 cases of renal cell carcinoma (RCC) were observed among about 66,000 patients on renal dialysis. Other case-reports and small case-series have been published. To evaluate the U.S. experience in this regard, we used a computer-based file maintained by the Epidemiology and Biostatistics Program for diagnoses at VA hospitals. We studied 17,246 black or white male veterans who survived their first dialysis admission in VA hospitals, 1969-1985. RCC was recorded on the inpatient charts of 118 patients: 44 were diagnosed before, 35 during and 39 after the first admission with dialysis. Our interest was in the last group. All but four of these charts were available for review, but we found that only 15 cases could be confirmed with the proper sequence of events, plus four clinically diagnosed patients without histological confirmation. An additional seven cases (ineligible for the study) were found under other cancer diagnoses. There was a statistically significant excess of RCC among blacks, but not among whites. The peak occurrence of RCC in VA patients was too soon after the initiation of dialysis to have been induced by exposure to the plastic tubing of the apparatus. It looks, instead, as if end-stage renal disease may lead to renal cysts, which progress to benign tumors and then undergo malignant transformation. Possibly end-stage renal disease due to hypertension predisposes to RCC. Our data on this point, though sparse, suggest that hypertension was more common among blacks than whites with RCC after dialysis. Hence, the greater frequencies of dialysis-associated RCC among Japanese as well as blacks may be due to their higher frequency and greater severity of hypertension. (The Japanese series included some benign tumors, whereas the VA series consisted only of malignant tumors, and there was under-ascertainment of cases.) A by-product of this study was the finding that there are many errors in the VA computer-based file, and chart review is required to correct them. Studies based only on the coded data may be misleading.

Keloids and tumors in Rubinstein-Taybi syndrome: In 1963, Rubinstein and Taybi described a syndrome of congenital malformations of the face, broad thumbs and mental retardation. Since then Dr. Rubinstein has seen 64 of these patients in referral, had personal communications concerning another 165, and screened the literature from which he gleaned another 345 cases. The occurrence of cancer and keloids, some of them spontaneous, was possibly excessive, so he asked us to help interpret these findings. The most substantial finding concerned 28 keloids, of which 6 were seemingly spontaneous. Three children with acute lymphocytic leukemia were in the series--of interest, but not clearly an excess. The other six malignant tumors were of diverse types, with no known feature in common. When combined with the benign tumors, nine of the 22 were noted to have arisen from cell rests. Developmental errors that lead to the syndrome may also have led to certain neoplasms.

Benign elevation of the alkaline phosphatase level: A lawyer for the Department of Health and Human Services consulted us about his 18-year-old son who had a flu-like disease, and when his college infirmary ordered a blood test, the usual battery of 12 blood chemistries was done. The alkaline phosphatase (ALP) level was markedly elevated. Usually this finding causes concern and a series of diagnostic tests in a search for cancer of the bone or liver is conducted. Brief questioning revealed that an older sister had gone through this experience when, at the age 11 year, her ALP level was found to be very high. Study of the family revealed no other member with comparably high ALP values. We learned that Dr. Mulivor, at the Coriell Medical Research Institute in Camden, N.J., fractionates ALP to determine from which organs it comes: liver, bone, placenta, kidney, and intestine, and has monoclonal antibodies to intestinal, placental and liver/bone/kidney ALP. The siblings with elevated levels had discordant findings, which suggested the influence of two genes. Our report of these findings has been published to explain current understanding of ALP, and to alert physicians to consider this benign genetic disorder as a diagnosis in young people.

Review articles: Drs. Pizzo and Poplack of the Pediatric Oncology Branch of NCI have published a comprehensive volume on pediatric oncology. Etiology is well covered with respect to the environment (Miller), genetics (Mulvihill) and prevention in pediatrics against cancers of adulthood (Li and Mulvihill). A main interest of the Branch has been to encourage clinical observations as clues to cancer etiology. The Japanese have been more receptive than others to this approach, and the 18th annual cancer symposium of the Princess Takamatsu Cancer Research Foundation was devoted to this subject. Almost all of the 28 speakers played a role in deriving etiologic clues from small series of rare events in cancer occurrence. The proceedings and a meeting report have been published.

International activities: The U.S.-Japan Cooperative Cancer Research Program provides another opportunity for exploring etiology through two workshops annually under the Interdisciplinary Area, the coordinators for which are Dr. Sugano of the Cancer Institute in Tokyo and Dr. Miller. The workshops held in the past year concerned:

- Cancer Registries, March 1989, in conjunction with the annual meeting of the American Association of Central Cancer Registries. Attended also by four Korean epidemiologists under the U.S.-Korea binational program.

- Biostatistics, November 1988, the third on this subject, to encourage development of this discipline in Japan. Co-organizers: Drs. Hoel (NIEHS) and Yanagawa (Fukuoka). Proceedings to be published.

A meeting report was published during the year concerning a 1988 workshop on the Li-Fraumeni syndrome, held to describe the U.S. experience and to search for cases among Japanese data collections, and the proceedings were published of a 1987 workshop on melanoma.

First steps were taken to enhance descriptive epidemiology in Korea, under the newly established U.S.-Korea Cooperative Cancer Research Program. Four

Korean epidemiologists attended the U.S.-Japan workshop on cancer registries, described above. A symposium on hospital-based registries was held in Seoul on June 28, 1989, co-organized by our Branch.

Pediatric Practitioner Research Award: To enhance appreciation of research suggested by clinical observations, Dr. Miller proposed that the American Academy of Pediatrics create an annual award for research by a pediatrician in practice. We hoped that other pediatricians would follow the examples set by the award recipients, and anticipated that both academicians and practitioners would become aware of the scope of research in practice. Dr. Miller chairs the selection committee. Now that four awards have been made, the impressive breadth and depth of office-based research has become apparent, and will be reviewed in an article for a wide audience.

Demography

Beginning in the mid-1960s, the Branch created a data file from death-certificate diagnoses for the eight million people who died of cancer in the United States from 1950 through 1982. This resource has been of continuous value in portraying the U.S. cancer experience in various ways. In the early years, volumes were published on mortality data according to the state of residence, followed by atlases on mortality by county or State Economic Areas. SEER data are now being used for incidence studies of special population groups and subclassifications of cancers.

Economic subregions: In a search for a method to aggregate regional mortality data that would improve on the use of State Economic Areas (N=506), which do not cross State borders, we experimented with the use of economic subregions (ESRs) (N=119) as defined by Bogue and Beale of the Bureau of the Census in 1961, and with the Bureau of Economic Analysis (BEA) areas (N=183), neither of which is confined by State boundaries. In each, counties are aggregated with respect to economic similarities. In the only application of ESRs to date, an excess of nasopharyngeal cancers among U.S. white males, 1950-1975, was found along the Gulf Coast in particular. No corresponding effect occurred among white females.

With Charles M. Croner of the National Center for Health Statistics, Frank W. McKay of our Branch mapped SMRs for nasopharyngeal cancer in Florida, 1953-1982, with respect to county, SEAs, ESRs and BEA areas. They found that regions with significantly high SMRs varied according to the economic grouping used:

Units	Number in State	High SMR	Location
Counties	133	4	2 North, 1 Mid*, 1 South*
SEAs	15	2	1 Mid*, 1 South*
BEA Areas	6	1	1 South
ESRs	3	1	1 North

* These two counties were large enough to be SEAs, so they appear in both categories.

Combining a high-rate county with various groups of its neighbors washed out the high SMR in some instances. The conclusion was that for this form of cancer, which is rare, the various units for mapping give different results depending on the configuration of the boundaries of the units. When used across State lines, however, new clues to geographic concentration across a broader area may appear, as along the Gulf Coast in this case.

Bureau of Economic Analysis areas: Experimental use of 181 economic areas defined in 1977 by the Bureau of Economic Analysis (BEA) of the Department of Commerce yielded maps with hot spots which, if studied by case-control studies, may point to environmental carcinogens as the cause of the high frequencies. Among the notable clusters are high rates of stomach cancer among males and females in the BEAs for Duluth, MN; Providence, RI; Wausau, WI; and Albuquerque, NM, among others. In Duluth, for example, from 1970-1980, 313 males died of stomach cancer as compared with 193 expected (SMR=162).

From 1979-1982, a cluster of 13 cases of Burkitt's lymphoma occurred among males in the BEA for Minneapolis-St. Paul. More recent data are needed, and a case-control study may point to a cause. In 1968-1982, high rates for cancer of the pleura (probably mesothelioma) were noted in males in the BEAs for Seattle; Buffalo; Rochester; Huntington, WV; and Norfolk, and for males and females in the area of Harrisburg, PA. Studies of the environmental exposures of these decedents may reveal previously unrecognized carcinogenic hazards, which can be prevented in the future.

One-third (6 of 18) of the BEA areas with highest rates for cancer of the lip also had the highest rates for cancer of the salivary gland. Waco, TX and Lexington, KY had not only high rates, but also a ratio of 1:1 for these cancers instead of two salivary for each lip cancer. The deaths generally were 40+ years of age. Further study may reveal the basis, if any, for the association between lip and salivary gland mortality in these areas.

The highest rates for cancer of the gall bladder were in areas with large Hispanic populations, a group known to be at higher risk than usual. Of the 18 areas with the highest rates, eight were high for both males and females, 1970-1980. Among the eight, those that did not have large Hispanic populations were Duluth; Eau Claire, WI; Minot, ND; Fargot, ND; and Erie, PA.

Mortality from cancer of the uterine cervix should be preventable through early detection and treatment. The national age-adjusted rate, 1970-1980, for U.S. whites was 6.48 deaths per million. In Brownsville TX the rate was 11.99, in Terre Haute IN 11.64, Huntington WV 11.58 and Charleston WV 11.07. Efforts toward prevention should be concentrated in these areas.

A high proportion of cancer of the urinary bladder is environmentally induced. Areas that showed the highest mortality rates among males included Providence, RI (16.30 per million); Burlington, VT (15.24); and Buffalo, NY (15.22). The national age-adjusted rate was 11.58 per million.

Finally, as previously shown by others, the northeast has the highest total cancer mortality in the country. The cancers responsible are mainly of the gastrointestinal tract, urinary bladder, lung and larynx, but surprisingly, in four of the eight areas, the mortality rates for Hodgkin's disease in one

or both sexes were in the top decile. A study will be made of the correlations among these cancers.

Radiation Effects

We draw upon our experience since the 1950s in writing and advising on the effects of ionizing and other forms of radiation on human health. This experience also serves as a basis for writing and advising on the health effects of chemicals on health.

Low-dose effects: Investigators continue to examine their data for the lowest dose at which a carcinogenic effect can be inferred. Some results reported by Radford et al. in 1983 on thyroid nodules following low-dose exposure prompted Dr. Boice of the Radiation Epidemiology Branch to investigate the possibility of a study of thyroid nodules in older women living in the high-background area of southeastern China. Dr. Beebe assisted in the development and conduct of the resulting study of 2,000 older women, 1,000 continuously exposed to 330 mR/yr to the thyroid, and 1,000 exposed to 114 mR/yr. Physical examinations were performed by U.S. specialists and laboratory work by Chinese scientists under a contract with the Laboratory of Industrial Hygiene, Ministry of Public Health, Beijing. Two papers are in preparation. There was essentially no evidence that nodular thyroid disease was elevated among the residents of the high-background area. Stable and unstable chromosome aberrations were increased among women in the high-background area, however, as was mild goiter.

General reviews of human health effects: Review papers have been written covering the current literature on human health effects of exposure to ionizing radiation, especially cancer, and on the specific findings of the Atomic Bomb Casualty Commission (ABCC) and its successor, Radiation Effects Research Foundation (RERF). Other reports have been published on the intrauterine effects of exposure to ionizing radiation, stressing the importance of small head size at very low doses. This effect, often ignored, is ten times more frequent than severe mental retardation, on which attention has been focused. Small head size should be looked for among those exposed in utero at Chernobyl.

Efforts to stimulate and guide research: The most fruitful source of information on radiogenic cancer is the experience of the Japanese A-bomb survivors with which Dr. Beebe has long been associated. He contributes to program planning by making specific research suggestions, reviewing research protocols, and recommending research strategy. This is done informally with members of the staff of the RERF through correspondence and occasional visits to Hiroshima and Nagasaki, consultation with Dr. Charles Land, Project Officer for the NCI contract with the National Academy of Sciences through which NCI funds are provided to RERF under a sub-contract, attendance at RERF workshops, and publications.

Members of the Branch attempted to stimulate work at RERF on the problem of individual susceptibility to the carcinogenic action of ionizing radiation. A pilot project was suggested under which subjects with and without cancer, and of high and low radiation doses, were studied in vitro for cell survival after radiation exposure to determine whether important differences could be

demonstrated in DNA repair mechanisms. Dr. Beebe participated in the 1988 RERF workshop on sensitivity to the effects of ionizing radiation on man and the 1989 RERF workshop on radiation carcinogenesis.

Dr. Beebe works closely with members of the Radiation Epidemiology Branch (REB), participating in staff meetings, review of manuscripts and protocols, and program planning generally. He also served as an assistant project officer on one REB project. He is a member of Dr. Boice's ad hoc advisory group on NCI participation in the studies of Japanese atomic bomb survivors. He continues to be in contact with the All-Union Scientific Centre of Radiation Medicine, USSR Academy of Medical Sciences, in Kiev and may play some advisory role in the epidemiologic studies of the effects of the disaster.

Liaison functions: As the HHS representative on the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) established by the Science Advisor to the President, Dr. Beebe participates actively in the deliberations of the Panel with respect to topics for which his epidemiologic expertise is especially relevant, and in facilitating communication between the Panel and elements of HHS, e.g., in reviewing draft work statements for subpanels, drafts of reports to be issued by the Panel, etc. Dr. Beebe's interest in planning for scientific exploitation of research opportunities offered by radiation disasters has led the Panel to establish a subpanel to consider this subject. He serves as a consultant to the subpanel. The Panel has considered the compensation issue, the effects of non-ionizing radiation, radon, the quality factor for neutrons, the validity of the collective dose concept, and many other topics. CIRRPC also provided the funds for the National Academy of Sciences to prepare the fifth report on the biological effects of ionizing radiation (BEIR V) and Dr. Beebe was one of those who represented the Science Panel at the deliberations of this committee. He is also a member of the sub-panel established to evaluate BEIR V and the 1988 United Nations report and prepare a synthesis that will serve the diverse interests of the concerned Federal agencies.

Advisory Committees: Activities concerning radiation effects involve consultations, serving on advisory committees and the integration of new information into analytical reviews concerning intrauterine effects and hematopoietic cancers. Consultations by Dr. Miller have mainly been with the Department of Energy, the Department of Justice and the Department of Labor (concerning cancers in government workers exposed to ionizing radiation) and the National Council on Radiation Protection and Measurements. Advisory committees include the Board on Radiation Effects Research (NAS-NRC), 2 years; the Science Council of the Radiation Effects Research Foundation in Hiroshima and Nagasaki, 9 years; Epidemiology Advisory Committees of the Hanford National Laboratory and the Los Alamos National Laboratory, 9 years; the University of Chicago Review Committee for the Biological, Environmental and Medical Research Division at Argonne National Laboratory, 2 years.

Chemical Pollutants

Dr. Miller served for five years as Chairman of the Advisory Committee for the Air Force's Ranch Hand Study of air and ground crews, many exposed heavily to Agent Orange sprayed as a defoliant in Vietnam. The Committee reported to the Domestic Policy Council's Agent Orange Working Group chaired by the Under Secretary, Department of Health and Human Services. The Committee provided substantial help to the Study in its preparation for periodic medical examinations and analyses of the findings, as well as annual evaluations of mortality data. When the Centers for Disease Control developed an assay in 1987 for measuring dioxin in the blood, Ranch Hand personnel were found to have elevated levels, whereas U.S. ground forces in Vietnam did not. The half-life for dioxin was shown in Ranch Hand personnel to be 7.1 years.

The study continues, but the Advisory Committee in the future must, in accord with new legislation, be chaired by a non-government scientist, and at least three members must be appointed from nominees submitted by veterans organizations. The NIH charter for the Committee was allowed to expire.

An important study of the intrauterine effect of polychlorinated biphenyls (PCBs) and their contaminants, proposed by Dr. Miller (Environ. Health Perspect. 60:211-214, 1985) was conducted in Taiwan by the National Institute of Environmental Health Sciences (NIEHS). Exposure of about 2,000 people had occurred in 1979, when cooking oil was contaminated during its manufacture by PCBs, used as a heat-transfer agent. This misadventure replicated one in Japan in 1968, where birth control made it impossible to study offspring who were conceived after the exposure. The NIEHS study revealed that neuroectodermal defects occurred not only among those in utero at the time, as previously recognized, but also in a substantial percentage of children conceived subsequently and exposed to PCBs that had been stored in the mothers' fat. For example, at birth 11 of 127 had teeth present as compared with none of 113 controls. On physical examination in April 1985, at 1-86 months of age, 11 of 101 had chipped teeth as compared with none of 100 controls. Other excess abnormalities of skin, nails and gingiva were noted, as well as delay in intellectual and behavioral development (Rogan et al. Science 241:334-336, 1988).

Hepatitis B virus (HPV) and primary hepatocellular carcinoma (PHC)

A serologic study was completed and published in the New England Journal of Medicine in 1987. Three groups were defined: I, men hospitalized in 1942 with post-vaccinal hepatitis; II, men vaccinated from contaminated lots of vaccine who did not become ill; and III, men who entered the Army only after the vaccine was withdrawn. The serologic examination of 597 men showed that the 1942 epidemic was caused by HBV. A cohort mortality study of about 60,000 men representing the same three groups is essentially finished and a manuscript is in preparation. Mortality from all causes was quite similar in the three groups, SMRs being .89, .87, and .88 for Groups I, II, and III, respectively. For all malignant neoplasms the parallel SMRs differed significantly, being .87, .77, and .85 in the same sequence. Deaths from cirrhosis were comparable for the three groups. There were 65 deaths coded to 155.0 (liver cancer, primary) and 155.2 (liver cancer, not specified as

primary or secondary). The three groups did not differ significantly with respect to these causes as coded from the death certificates. From a blind review of all available pathology material a small excess of definite PHC deaths emerged that seems inconsistent, in its size, with generally held views of the likelihood that HBV infection will generate the carrier state and the likelihood that a carrier will develop PHC. Although other interpretations may be possible, the results of the cohort study strongly suggest that the relationship between PHC and HBV infection depends on age at infection. Adults infected with HBV appear to have low carrier rates and perhaps also low transition probabilities from the carrier state to PHC.

A case-control investigation has progressed least among the three arms of the study. The planned data collection has been completed and is being prepared for analysis. A major disappointment has been the poor quality of VA hospital diagnoses of PHC. It has been possible to verify diagnoses for less than half the cases in the VA diagnostic index of hospitalizations and the process of verification has been tedious and burdensome. Only 24 valid cases of PHC could be identified among Army WW II veterans who entered service prior to April 1942, and whose records of yellow fever vaccination could be retrieved in St. Louis. Controls have been selected and matched on a 2:1 basis with regard to hospital, discharge date, year of birth, sex, and race. This arm of the study will have far less power than anticipated in 1983 when it was planned.

Development of Data Resources for Epidemiology

Many epidemiologic studies depend on the availability of current addresses for the subjects to be studied. Critically important resources for the Program include those of the Health Care Financing Administration (HCFA), the Social Security Administration (SSA), and the Internal Revenue Service (IRS). SSA has now been persuaded to join HCFA in its willingness to provide addresses from its own beneficiary files and, in response to changes in the agreement between IRS and the National Institute for Occupational Safety and Health (NIOSH) requested by NCI, has agreed to provide Social Security Account numbers for use by IRS in providing addresses for occupational studies performed by investigators in the Department of Health and Human Services. Efforts continue to amend the legislation that limits access to IRS addresses to NIOSH investigators of occupational factors in disease. A legislative proposal has been drafted but opposition by the Treasury Department has thus far blocked it. Should it be possible to expand access to IRS address files beyond the domain of occupational studies, an incidental benefit would be additional information on mortality.

Occupational histories: Because occupational histories obtainable from next-of-kin are of questionable completeness and reliability, and SSA has been collecting information of registrants' places of employment since 1935, an effort has been made to compare information in SSA files with that obtained after death and from next-of-kin. It soon became clear that the arrangement of SSA files made the necessary searches far too expensive for most investigations. The pilot project undertaken by SSA and NCI to explore the agreement between the two sources of employment information is nearing

completion. It is expected to show that the agreement is very poor primarily because the SSA files contain so many more jobs than the next-of-kin can recall. It also appears that SSA files do not clearly identify multi-unit employers whose reports fail to allocate their employees to their specific places of employment but merely report them as employees of the multi-unit firm wherever its head offices are located. Multi-unit employers who voluntarily report by unit are identified.

Because U.S. vital statistics have not been extended to the reporting of mortality in relation to occupation and industry of employment, several efforts have been mounted to explore the possibility of creating a national system that might be useful for surveillance and hypothesis-generation. These efforts have centered around two possibilities: (1) state coding of death certificate information coupled with reporting to NCHS for analysis and publication; and (2) exploring the utility of the SSA Continuous Work History Sample, a one percent sample of SSA registrants. NCI has joined NIOSH in funding a program under which states are encouraged to perform industry and occupation (I/O) coding in a standard way, their coders are trained in procedures developed for the program by the Census Bureau, states are paid a unit fee for the coding, and NCHS performs a quality-control function as well as collating the material for analysis. NCI support was scheduled to terminate last year, when it was anticipated that NCHS would have the funds with which to carry the program forward to completion, but it now appears that NCI funding will be required for two more years. 1984 I/O files from 12 states have been put together by NCHS and extend to 270,000 records for ages 20 and older. For 1986 the files of 18 states are available, amounting to 517,000 records. A draft report for 1984 has been prepared by NIOSH and NCHS statisticians and Ms. Madigan, our statistician, is exploring the file in an effort to learn how it might be processed most usefully for the Program.

Collaborative pilot work with IRS and SSA to explore the potential of their files is nearing completion. Under an interagency agreement with NCI, IRS has shown that it can code the occupational entry on the IRS Form 1040, provided that it has information on industry from SSA. Presently, under a second interagency agreement with NCI, IRS is processing a file of about 260,000 taxpayers in 1979 with about 18,000 deaths in an effort to learn whether the addition of its information on occupation to that of SSA on industry would provide insight into cause-specific mortality beyond that obtainable from tabulations confined to industry of employment. Should it appear that the IRS information on occupation does have this capacity, consideration could be given to strengthening the Continuous Work History Sample (CWHS) file with the addition of the IRS information on occupation. Fortunately, IRS now has its own reasons for wanting to code its occupational information, a fact that may eventually lead to some improvement in its quality, which is now only fair.

Under another interagency agreement with NCI, SSA has obtained death certificates for about 90,000 deaths in the CWHS during the 1973-1977 interval. Cause of death has been obtained from NCHS and I/O coding of death certificates has been done by Census. The file is now ready for analysis. The plan is to test the file by seeking well-known cause-specific mortality differentials by industry of employment. If the results are positive, consideration might be given to an extension of the time period in

order to increase the power of any search for differential mortality. A particular feature of the CWHS is its historical information on industry of employment starting in 1957. At present the file is being studied for useful ways of patterning these histories.

Both the IRS and the SSA death certificates on file will permit a comparison of the I/O information on the death certificate with that in IRS-SSA or SSA files. The comparison with the longitudinal histories in the SSA files should be especially useful. At present there is very little information on the meaning of the I/O information placed on death certificates in the 50-odd jurisdictions where the records are generated, and if we are going to add this information to the national vital statistics system, thought must be given to criteria for making the entries and to quality control.

National Death Index: Dr. Beebe continues to serve as one of the NIH advisors to the Director, National Center for Health Statistics, in connection with the operation of the National Death Index (NDI). Together with Dr. Boice, chief of the Radiation Epidemiology Branch, and others, he has actively promoted investigation of the feasibility and cost of retrofitting the present NDI that begins with deaths in 1979. With the aid of a contractor and the Association of Vital Records and Health Statistics, NCI has learned that the cost of extending the NDI back to 1960 would be about 19 million dollars, primarily because the files of the states are not completely on tape for that period and their formats vary greatly. With the limited funds available to NCI, including those volunteered by other agencies, the NDI can probably be extended back no farther than 1977. Negotiations over cost are still in progress. Dr. Beebe also chairs the NCI Working Group on the NDI that is proposing procedures under which investigators would be required to store identifying information on subjects of study whenever it seems likely that future application to the NDI for mortality searches will be forthcoming.

CLINICAL STUDIES SECTION

This unit of the Branch has been located in Boston since 1953, where it has had access to a wide array of etiologically interesting cases in the clinics and on the wards. Specimens collected from these patients have created opportunities to collaborate with laboratory scientists in studies of the pathogenesis of human neoplasia, with particular attention to the role of recessive oncogenes. In the past year, Dr. Judy Garber has continued to work in the Section as an Epidemiology Research Fellow, and Dr. Arlene Kantor has transferred to the Section from the Environmental Epidemiology Branch. In recent years, research based upon our observational research has attracted students, physicians in training and other health professionals to work with us. Currently these include Drs. Jim Talcott and Fred Kass, medical oncology fellows at the Dana Farber Cancer Institute.

Hereditary/Familial Cancer Syndromes

Hereditary renal cancers in children and adults: Studies of the association of Wilms' tumor with aniridia or with hemihypertrophy have led to a search for Wilms' tumor genes on the short arm of chromosome 11. We have recently

reported in Nature that a linkage analysis of a family with 7 children having Wilms' tumor has excluded chromosome 11p as the locus of a "familial Wilms' tumor gene," and a search for this locus has been initiated. In addition, studies of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8 have shown that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3, but that c-myc is not within 700 Kb of the breakpoint. Studies of chromosome 3 by us and others have shown chromosome 3p rearrangements in renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. Several techniques are now being used to clone the breakpoint on chromosome 3 in our family.

The familial breast cancer-sarcoma syndrome: Several new studies have been made on this syndrome, originally described in 4 families by Li and Fraumeni. Recent analysis of 24 affected families has clarified the clinical features of this syndrome: sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. A prospective study of new cancers among family members since initial ascertainment shows that about 30 percent of cancer survivors in the family have developed second neoplasms on follow-up observation. Investigations are in progress of 13 additional families that appear to have the syndrome. Cytogenetic studies of soft tissue sarcomas showing correlations between chromosomal translocation and histological subtype of the sarcoma are being pursued in work in progress to clone the X;18 translocation in synovial sarcoma.

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, Dr. Garber has recently found and reported 11 families with polyposis associated with childhood hepatoblastoma, a newly described association. We have established a registry of the hepatoblastoma-polyposis coli association and have begun collection of specimens for laboratory studies. We have recently observed 5 cases of multiple primary cancers that include melanoma and soft tissue sarcoma. Two of them also have dysplastic nevus syndrome (DNS). Dr. Garber is examining the possibility that sarcomas are a previously unrecognized feature of dysplastic nevus syndrome.

Mesothelioma in cigarette filter makers: Clinical observations can identify cancer clusters due to potent environmental carcinogens. We recently observed mesothelioma in 3 men who had made cigarette filters which contain asbestos, particularly highly carcinogenic blue asbestos, or crocidolite. An additional 33 workers at this plant have been identified and on follow-up 5 deaths from mesothelioma, 7 from lung cancers, and 5 from asbestosis were found.

Late Effects in Survivors of Childhood Cancer

In a 14-year follow-up of patients previously studied for the occurrence of second cancers at the Dana-Farber Cancer Institute, 23 new cancers were observed when 2 were expected. All but 2 of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The findings indicate that the high risk of second neoplasms among childhood cancer survivors extends far into adult life.

A recent study reported a 90% risk of second cancers, primarily sarcomas, among nearly 800 survivors of hereditary retinoblastoma. To re-assess the risk, a follow-up study of these cases and 1200 others with retinoblastoma is in progress. The study has provided access to tissue of second cancer in retinoblastoma patients. These tissues are being probed for loss of the retinoblastoma gene.

The frequency of hypertension has been studied in a series of Wilms' tumor patients who had nephrectomy and other treatments between 14 and 53 years ago. Eighty percent are normotensive. The overall frequency of hypertension did not exceed expectation based on data for the general population. The data provide assurance that hypertension is not a common sequelae of treatment for Wilms' tumor. We now plan to study renal function in those patients who had nephrectomy and abdominal radiotherapy in childhood.

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 and through clinical observations at the bedside. With informed consent, epidemiologic inquiries are made to identify predisposing host and environmental factors, and to quantify the risk of cancer development. Concurrent laboratory studies are made to clarify biologic mechanisms of cancer susceptibility. Results show that carriers of cancer genes develop cancer at high rates in specific tissues, including multiple primary cancers in childhood. Work is in progress to map several of these recessive oncogenes, including genes for renal carcinoma, familial Wilms' tumor, and the dominantly inherited syndrome of breast cancer, sarcomas and other childhood neoplasms. 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 2000 survivors of childhood retinoblastoma in New York and Boston are being examined for the role of inherited susceptibility and ionizing radiation therapy in the development of second cancers.

CLINICAL GENETICS SECTION

Cancer Genes: Interdisciplinary Collaborations

The neurofibromatoses: The neurofibromatoses consist of two major clinically and genetically distinct disorders: von Recklinghausen's disease (neurofibromatosis type 1, also called NF1) and bilateral acoustic neuroma syndrome (neurofibromatosis type 2, called NF2).

NF1 is a common autosomal dominant disorder which affects some 100,000 persons in the United States; its protean manifestations impinge on almost every body organ and include an increased risk of developing certain cancers. In an international effort to map NF1 precisely, several clinician-investigators, including Drs. Parry and Mulvihill, and laboratory scientists joined forces to form the NF1 Linkage Consortium. Consortium members agreed to exchange DNA probes for use in examining DNA from NF1 families and then to submit their RFLP data to one center for a combined analysis. As the coordinators of some of these activities, Drs. Parry and Mulvihill established guidelines for RFLP coding, prepared and distributed coding sheets

for recording data, received all data, checked it for errors, and compiled it on diskettes which were returned to the submitters for their analysis. In the combined data set, there was no evidence of locus heterogeneity; these data (13,838 genotypings on 31 markers in members of 142 NF1 families with 700 affected individuals) were then subjected to multipoint linkage analysis which confirmed that NF1 is just proximal to the centromere on 17q and flanked by several polymorphic markers the closest of which span an estimated distance of about 3 cM. The results confirm that a single locus is responsible for the NF1 phenotype. Supported by the very rapid progress made in the fine mapping of NF1, the gene will soon be isolated.

A common perception of NF1 is that cognitive dysfunction and other developmental disabilities are present in up to 40 percent of affected individuals. However, no rigorous, controlled neuropsychological assessment had addressed this issue. We therefore collaborated with staff from the National Institute of Neurological and Communicative Disorders and Stroke and other members of the Interinstitute Medical Genetics Program in a pilot study to assess subtle neurologic abnormalities, impaired cognitive function and developmental disabilities in children and young adults with NF1. Thirteen pairs of siblings, aged 6 to 26 years, were evaluated, based on diagnostic criteria specified in advance. One subject in each pair had NF1 while the other, the control subject, was unaffected. Subjects with a documented or suspected developmental disability which led to the original diagnosis of NF1 were excluded as were any individuals with evidence of focal nervous system disease. Overall, the 13 NF1 subjects had no excess of mental retardation, attention deficit disorder or specific learning disabilities. However, they had significantly more subtle neurologic abnormalities and significantly lower full-scale IQ scores than their unaffected siblings. In addition, an unusual visual spatial-orientation deficit was present in eight of nine affected subjects. Although a specific cognitive deficit was not identified in the subjects with NF1, our findings suggest that individuals with this condition have a widespread alteration of the brain during development that results in mild neurologic and cognitive abnormalities.

As for the other neurofibromatosis, NF2, our initial studies focused on one large three generation kindred. Twenty-four family members over age 18 underwent comprehensive examinations that included audiology, auditory brainstem-evoked responses (ABRs), ophthalmology and brain magnetic resonance imaging (MRI). The examined individuals included six with previously diagnosed acoustic neuromas and 18 of their sibs or offspring who each had a 50 percent risk of NF2. The major finding was confirmation of the possibly pathognomonic feature of premature posterior subcapsular lens opacities. The cataracts are an important early sign of the presence of the NF2; how one mutant gene gives rise to such pleiotropic effects is unknown, but it is intriguing that the gene for a lens protein is on the same chromosome as the NF2 gene. Other preliminary findings are: a) acoustic neuromas were identified by MRI in 4 of 18 at-risk relatives, aged 19 to 70 years. The smallest tumor that could be visualized was a 5 mm intracanalicular mass. b) ABRs were abnormal in several individuals who had acoustic neuromas but no hearing loss; this finding suggests that ABRs are more useful than audiology in assessing early loss of eighth nerve function. c) Among individuals with acoustic neuromas, hearing loss correlated more consistently with increasing age than with increasing tumor size, an important fact when considering surgical intervention.

Cancer Families, Chromosomes, Syndromes, and Synthesis

Multiple endocrine neoplasia syndrome (MEN1): In addition to NF1 and NF2, we are attempting to map other preneoplastic mendelian disorders through interdisciplinary family studies. Consultation by an endocrinologist of the National Institute of Diabetes and Digestive and Kidney Diseases provided access to 68 members of a large kindred with MEN1 and long-term follow-up with definitive biochemical evaluation. While we were collecting specimens for random DNA markers, a Swedish team independently proposed assignment of the gene to chromosome 11. Because affected patients circulate a basic fibroblast growth factor-like substance in their plasma, we chose to genotype through linkage studies a related gene known to be localized to 11q13 in addition to two anonymous DNA markers. The candidate gene locus, INT2, was found to be closely linked to the MEN1 gene with a lod score of 3.55 at a recombination frequency of 3.5 percent.

Studies of sister chromatid exchanges (SCEs): We designed laboratory experiments to establish a basis for increased epidemiologic use of the cytogenetic phenomenon of SCEs which is a marker of population exposure to certain mutagens and is constitutionally elevated in Bloom's syndrome, which predisposes to certain malignancies. Genetic epidemiologists in our program and elsewhere have repositories of cryopreserved lymphocytes, but most published experience with SCEs is with fresh whole blood cultures. Our design correlated spontaneous and mutagen-induced SCEs in fresh and frozen specimens from the same persons. In addition to spontaneous rates of SCEs, frequencies were evaluated following in vitro exposure to three standard mutagens. Purified lymphocytes had consistently and significantly higher baseline frequencies than did cells from whole blood cultures and were more sensitive to N-methyl-N'-nitro-N-nitrosoguanidine and 4-nitroquinoline 1-oxide. The response to mitomycin C was similar in all culture types. There was, overall, no consistent effect of freezing on baseline or induced SCE frequencies in the purified lymphocytes. We concluded that purification and cryopreservation of human lymphocytes do not alter the baseline or mutagen-induced SCE response and, in certain epidemiological, occupational and monitoring situations, may have logistical and technical advantages over the use of fresh whole blood. It was further determined that repair of mutagen-induced lesions was likewise not altered by purification or cryopreservation of lymphocytes.

Melanoma: SCEs were one of several cytogenetic phenomena evaluated in 163 family members from 13 families with melanoma complicating the dysplastic nevus syndrome. No clonal cytogenetic abnormalities were observed. Compared to pooled controls, i.e., normal family members and spouses, subjects with the dysplastic nevus syndrome, with or without melanoma, had increased frequencies of numeric abnormalities and those with melanoma had an excess of major (but not minor) structural abnormalities. 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 SCEs. Our suggestion that chromosomal instability contributes to the pathogenesis of hereditary melanomas was rapidly confirmed by independent investigators.

Interinstitute Medical Genetics Program

In support of many of the above efforts, Drs. Mulvihill and Parry continue to direct the NIH Interinstitute Medical Genetics Program including its clinical services and training program for 10 Fellows and 12 medical students. Actual numbers of patients seen who had or were predisposed to neoplasia were:

Neurofibromatosis type 2	30
Neurofibromatosis type 1	21
Hypereosinophila syndrome	5
Women at high risk of breast cancer	4
Nevoid basal cell carcinoma syndrome	3
von Hippel-Lindau's disease	3
Familial leukemia	2
Other familial cancers	5
Lymphedema with lymphangiosarcoma	1
Pancreatic cancer	1
Sarcoma	1
Squamous cell carcinoma	1
Tuberous sclerosis	1
Ruvalcaba-Myrhe-Smith's syndrome	1
TOTAL	79

Reproductive, Genetic, and Other Consequences of Cancer and its Treatment

Between 1980 and 1983, we interviewed 2283 survivors and 3270 of their siblings as controls about their own health, their reproductive experiences and the health of their children. Survivors were diagnosed between 1945 and 1975; they had to have survived more than five years after the diagnosis of their first malignancy and to have reached age 21.

Knowledge of cancer: When we asked our survivors if they had ever had cancer, 14 percent of survivors of malignancies at sites other than the brain and central nervous system did not know that they had been diagnosed with a cancer. Survivors who were unaware of their cancer history were more likely to be non-white, to have been diagnosed in earlier years, not to have received alkylating agent therapy and, among our five registries, to have come from Connecticut. Because of the seriousness of many late effects, such as second cancers, complications of pregnancy and infertility, these findings emphasize the importance of adequate counselling for patients and families.

Education: Overall, educational achievement was similar in cancer survivors as compared to controls, with one exception. Survivors of tumors of the brain and central nervous system were less likely to complete eighth grade or, if they completed high school, to enter college.

Marriage: Male survivors were 20 percent less likely to marry than male controls; female survivors had only a slight marriage deficit. Survivors of brain and central nervous system tumors were substantially less likely to marry, men even less so than women. Diagnosis at ages under 10 years significantly reduced the marriage rate in male central nervous system tumor survivors from an already low ratio of 0.46 to an even lower ratio of 0.31. There were no differences in divorce rates overall and, among women, no differences by site or age at diagnosis. However, men who had been diagnosed and treated for brain tumors before the age of 10 or who had survived retinoblastoma were significantly more likely to have their first marriages break up than male controls.

Pregnancy after Wilms' tumor: Following up on an observation by an international collaborative group headed by Dr. Li, we examined the pregnancy outcomes among our survivors of Wilms' tumors and confirmed and extended his findings. Pregnancies in female survivors of Wilms' tumor were four times more likely than pregnancies of female controls to end adversely; i.e., in a miscarriage, a low birth weight baby, a baby born with a birth defect, or a neonatal death. Further, we were able to extend these observations by pointing out the presence of bicornuate uterus in two female survivors and the sister of another. This malformation, probably a previously unrecognized birth defect associated with Wilms' tumor, accounted for recurrent miscarriages in one woman and sterility in two others. In other words, the full extent of the malformations associated with this cancer had not previously been noted since patients had not been studied during their reproductive years. Li et al. speculated that radiation damage to the developing uterus might impede normal pregnancy, causing early delivery, low birth weight, and an increased risk of neonatal death. Some infants in our series had a variety of minor birth defects which were compatible with intrauterine constraint, lending support to the idea of radiation damage. These data indicate the difficulty of separating the effects of the tumor from the effects of treatment in some circumstances and strongly support the policy of prolonged follow-up and counselling of survivors of this tumor.

Other preliminary results: Some preliminary analyses have been conducted (and presented at national meetings) on other areas of this large source of information.

- Survivors of brain tumors and tumors of the central nervous system had significant deficits in many aspects of living, including hearing and sight. They were more likely to report their health as poor than controls. In each of these areas, men were more likely to report doing worse than women.

- Despite their high risk for having another cancer, childhood cancer survivors had almost the same smoking habits as controls and the general population. Survivors treated with radiotherapy to the chest were more likely to have given up smoking, possibly due to chest disease after radiotherapy which was made worse by smoking.

- Menopause occurred earlier in female survivors compared to controls. Risk factors were genital cancers and treatment with radiation below the diaphragm, with or without alkylating agents. The risk of menopause was highest immediately upon treatment, but did not seem to fall off as time since therapy increased.

- Offspring of men and women treated for childhood and adolescent cancer were not more likely to be born with birth defects than offspring of their siblings.

- Among first pregnancies conceived after diagnosis, there was little suggestion of an excess of spontaneous fetal deaths in survivors. However, pregnant female survivors were more likely to have had an induced abortion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04377-18-CEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters 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
	P. Madigan	Health Statistician	CEB	NCI
	F. P. Li	Chief, Clinical Studues	CEB	NCI

COOPERATING UNITS (if any)

UCLA (R. Sparkes); 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. In an international collaborative effort to follow up the prior assignment of the gene for neurofibromatosis 1 to chromosome 17, we contributed to and helped compile data on 13,800 genotypings for 31 DNA markers in 142 families with 700 affected persons. Multipoint analysis identified two flanking markers, pHHH 202 and EW206, which had 95 percent upper confidence limits of 4 and 9 cM, respectively, from the disease gene locus, as close as markers now in clinical use for cystic fibrosis. The first confirmatory report was made of the assignment of the gene for multiple endocrine neoplasia type 1 to chromosome 11, with demonstration of its linkage to the gene INT2. In an effort to make assays of sister chromatid exchanges feasible for use by genetic epidemiologists, the phenomenon was compared in whole blood, separated fresh lymphocytes, and cryopreserved lymphocytes with and without in vitro exposure to known mutagens. Predictable, systematic differences in response were documented.

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
P. Madigan	Health Statistician	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 map preneoplastic disease genes and to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biological 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 comprise II reports of original research, 10 reviews, and three abstracts for national meetings. Research reports involved co-authors from the Environmental Epidemiology Branch, and Laboratory of Biochemistry of the National Cancer Institute; the National Eye Institute; the National Institute of Child Health and Human Development; the National Institute of Diabetes and Digestive and Kidney Diseases; the University of California at Los Angeles; the University of Utah; the University of North Carolina; Yale University; Harvard University; Boston University; Duke University; the Georgetown University Biomedical Ethics Center; the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders and the Clinical Center; Belvedere Medical Center, Carisle, PA; Westat, Inc.; Collaborative Genetics, Inc., Hazelton Laboratories, Inc.; the Merck Institute; and the Coriell Institute for Medical Research.

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.

Genetic Linkage of Neurofibromatosis 1:

In an international effort to map NF1 precisely, several clinician-investigators, including Drs. Parry and Mulvihill, and laboratory scientists joined forces to form the NF1 Linkage Consortium. Consortium members agreed to exchange DNA probes for use in examining DNA from NF1 families and then to submit their RFLP data to one center for a combined analysis. As the coordinators of some of these activities, Drs. Parry and Mulvihill established guidelines for RFLP coding, prepared and distributed coding sheets for recording data, received all data, checked it for errors, and compiled it on diskettes which were returned to the submitters for their analysis. In the combined data set, there was no evidence of locus heterogeneity; these data (13,838 genotypings on 31 markers in members of 142 NF1 families with 700 affected individuals) were then subjected to multipoint linkage analysis which confirmed that NF1 is just proximal to the centromere on 17q and flanked by several polymorphic markers, the closest of which span an estimated distance of about 3 cM. The results confirm that a single locus is responsible for the NF1 phenotype; the markers have already been utilized for prenatal diagnosis in one informative NF1 family. Supported by the very rapid progress made in the fine mapping of NF1, the gene will soon be isolated.

Clinical history of neurofibromatosis 1--Cognitive function:

Another common perception of NF1 is that cognitive dysfunction and other developmental disabilities are present in up to 40 percent of affected individuals. However, no rigorous, controlled neuropsychological assessment had addressed this issue. We therefore collaborated with staff from the National Institute of Neurological Disorders and Stroke and other members of the Interinstitute Medical Genetics Program in a pilot study designed to assess subtle neurologic abnormalities, impaired cognitive function and developmental disabilities in children and young adults with NF1. Thirteen pairs of siblings, aged 6 to 26 years, were evaluated; based on diagnostic criteria specified in advance, one subject in each pair had NF1 while the other, the control subject, was unaffected. Subjects with a documented or suspected developmental disability which led to the original diagnosis of NF1 were excluded as were any individuals with evidence of focal nervous system disease. Overall, the 13 NF1 subjects had no excess of mental retardation, attention deficit disorder or specific learning disabilities. However, they had significantly more subtle neurologic abnormalities and significantly lower full-scale IQ scores than their unaffected siblings. In addition, an unusual visual spatial-orientation deficit was present in eight of nine affected subjects so evaluated.

Although a specific cognitive deficit was not identified in the subjects with NF1, our findings suggest that individuals with this condition have a widespread alteration of the brain during development that results in mild neurologic and cognitive abnormalities.

History of neurofibromatosis:

As part of Dr. Mulvihill's role in opening the 1987 NIH Consensus Development Conference on the Neurofibromatoses (see below), ancient relevant texts were retrieved. Ms. Madigan prepared an exhibit consisting of three large posters illuminating NF1 research in history, for the benefit of conference participants and the NIH community. This led to a series of historical articles for the journal Neurofibromatosis. The exhibit included prints from von Recklinghausen's landmark monograph (1882), the earliest known English case report by Akenside (1768), early European reports (in Monstrorum Historia, Bologna, 1642 and "Case History of Extraordinarily Unsightly Skin," Leipzig, 1793) and a medieval pattern book from a monastery in Rein, Austria (c. 1200). Recognition of café-au-lait spots, Lisch nodules, and gene assignment to chromosome 17 were highlighted and outlined in a historical time line.

Other involvement in neurofibromatosis 1:

Dr. Mulvihill has written on the history of the disorder for both scientists and the public, reviewed research grants submitted to the National Neurofibromatosis Foundation, participated in workshops to clarify nomenclature and the etiology and management of optic glioma, and was involved in planning the NIH Consensus Development Conference on Neurofibromatosis at which he delivered the keynote overview lecture. He also continues to write a Neurofibromatosis Research Newsletter. Both he and Dr. Parry have been involved in research meetings sponsored by the National Neurofibromatosis Foundation and the local mid-Atlantic chapter, Neurofibromatosis, Inc. Dr. Mulvihill is a member of the Medical Board of the latter organization.

Clinical history of neurofibromatosis 2 (NF2):

Our initial studies focused on one large three generation kindred with NF2. Twenty-four family members over age 18 underwent comprehensive examinations that included audiology, auditory brainstem-evoked responses (ABRs), ophthalmology and brain magnetic resonance imaging (MRI). The examined individuals included six persons previously diagnosed with acoustic neuromas and 18 of their sibs or offspring who each had a 50 percent risk of NF2. Major findings were: a) acoustic neuromas were identified by MRI in 4 of 18 at-risk relatives. The affected individuals ranged in age from 19 to 70 years. The smallest tumor that could be visualized was a 5 mm intracanalicular mass. b) Posterior subcapsular lens opacities, a newly recognized manifestation of NF2, were present in eight of nine individuals with acoustic neuromas and intact lenses. Since the opacities had developed by age 19 in one and were present in three others under age 40, they may be one of the first signs of NF2. c) ABRs were abnormal in several individuals who had acoustic neuromas but no hearing loss; this finding suggests that ABRs are more useful than audiology in assessing early loss of eighth nerve

function. d) Among individuals with acoustic neuromas, hearing loss correlated more consistently with increasing age than with increasing tumor size, an important fact when considering surgical intervention.

Other preneoplastic genes. Neurofibromatosis 1 and 2 are not the only preneoplastic mendelian disorders we are attempting to map through interdisciplinary family studies. Consultation by an endocrinologist of the National Institute of Diabetes and Digestive and Kidney Diseases provided access to 68 members of a large kindred with multiple endocrine neoplasia 1 and long-term follow-up with definitive biochemical evaluation. In the course of our collection of specimens for random DNA markers, a Swedish team proposed assignment to chromosome 11. Because affected patients circulate in their plasma a basic fibroblast growth factor-like substance, we chose to genotype in linkage studies a related gene known to be localized to 11q13 in addition to two anonymous DNA markers. The candidate gene locus, INT2, was found to be closely linked to the MEN1 gene with a lod score of 3.55 at a recombination frequency of 3.5 percent.

In pursuit of this gene and its mechanism of tumorigenesis, we are collecting DNA from families with atypical multiple endocrine neoplasia 1, tumors known to complicate the syndrome, and tumor specimens from one family with the rare parathyroid carcinoma. As part of a national gene mapping workshop, we conducted two-point linkage analysis on four genes on the short arm of chromosome 11, including an oncogene and the locus for the Miller syndrome of aniridia and 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.

Sister chromatid exchanges. We designed laboratory experiments to establish a basis for increased epidemiologic use of the cytogenetic phenomenon of sister chromatid exchanges which is a marker of population exposure to certain mutagens and is constitutionally elevated in Bloom's syndrome, which predisposes to certain malignancies. Genetic epidemiologists in our program and elsewhere have repositories of cryopreserved lymphocytes, but most published experience with sister chromatid exchanges is with fresh whole blood cultures. Our design correlated spontaneous and mutagen-induced sister chromatid exchanges in fresh and frozen specimens from the same persons. In addition to spontaneous rates of sister chromatid exchanges, frequencies were evaluated following in vitro exposure to three standard mutagens. Purified lymphocytes had consistently and significantly higher baseline frequencies than did cells from whole blood cultures and were more sensitive to N-methyl-N'-nitro-N-nitrosoguanidine and 4-nitroquinoline 1-oxide. The response to mitomycin C was similar in all culture types. There was, overall, no consistent effect of freezing on baseline or induced sister-chromatid exchanges frequencies in the purified lymphocytes. We concluded that purification and cryopreservation of human lymphocytes do not alter the baseline or mutagen-induced sister chromatid exchange response and, in certain epidemiological, occupational and monitoring situations, may have logistical and technical advantages over the use of fresh whole blood. It was further determined that repair of mutagen-induced lesions was likewise not altered by purification or cryopreservation of lymphocytes. Sister chromatid exchanges were one of several cytogenetic phenomena evaluated in

163 family members from 13 families with melanoma complicating the dysplastic nevus syndrome. No clonal cytogenetic abnormalities were observed. Compared to pooled controls, i.e., normal family members and spouses, subjects with the dysplastic nevus syndrome, with or without melanoma, had increased frequencies of numeric abnormalities and those with melanoma had an excess of major (but not minor) structural abnormalities. 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. Our findings of chromosomal instability that may contribute to the pathogenesis of hereditary melanomas were rapidly confirmed by independent investigators.

Synthesis. Comprehensive reviews of various aspects of cancer genetics were published: the genetics of childhood cancer and the childhood origins of adult cancer for a large textbook of pediatric oncology, neurofibromatosis overview for a manual on the disorder, the genetics of lung cancer for a large medical genetics text, cancer control for a special issue of Clinical Genetics, and five articles for a mammoth Birth Defects Encyclopedia.

Resources. Two major contracts continued to provide nationally recognized laboratory expertise for our collaborations on radiosensitivity mechanisms of carcinogenesis and for epidemiologic research support services. (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, an FAES course, NIH Research Day, the NIH Epidemiology Committee, the Office of Human Genome Research, three workshops of the National Neurofibromatosis Foundation and Neurofibromatosis, Inc., Suburban Hospital (Bethesda), the Washington Dermatology Society, the University of Massachusetts, the University of North Carolina, the Johns Hopkins Oncology Center, the Medical College of Virginia, and the University of Pittsburgh. A visiting professorship was held at Pacific Presbyterian Medical Center, San Francisco; a memorial lecture at the Institute of Medical Genetics, Copenhagen; and invited lectures at the International Congress of Environmental Mutagens and the American Society of Preventive Oncology. At NIH, a Clinical Center Combined Staff Conference on Neurofibromatosis was conducted (and intended for publication in the Annals of Internal Medicine) and a distinguished Medicine for the Layman Series lecture was given on familial cancer. Abroad, lectures were given in Riyadh, Kingdom of Saudi Arabia, Gaslini Institute, Genoa, the European School of Medical Genetics, and the Department of Medical Genetics, Oslo.

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; to the Medical Advisory Board of the National Neurofibromatosis Foundation; to Editorial Boards of Genetic Epidemiology, Teratology, Cancer Investigation,

Clinical Genetics, Neurofibromatosis, and a new journal, Genes, Chromosomes and Cancer; as well as to various NCI and NIH committees. Critical reviews of manuscripts were prepared for the American Journal of Human Genetics, Trends in Genetics, Journal of Clinical Oncology, Radiation Effects Research Foundation, American Journal of Medical Genetics, 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 National Foundation-March of Dimes, and the National Institute of Dental Research.

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CONTRACTS IN SUPPORT OF THIS PROJECT

HEALTH RESEARCH INC., ROSWELL PARK MEMORIAL INSTITUTE (NO1-CP-71018)

Title: Genetic Factors in Persons at High Risk of Cancer: Solid Tumor Chromosome Analysis

Current Annual Level: $41,501

Person Years: 0.8

MEMORIAL SLOAN KETTERING HOSPITAL FOR CANCER AND ALLIED DISEASES (NO1-CP-71126)

Title: Genetic Factors in Persons at High Risk of Cancer: Solid Tumor Chromosome Analysis

Current Annual Level: $55,135

Person Years: 1.0

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

Major Contributions:

In the first one and one-half years of the present contracts, work has continued on the cytogenetics of sarcomas, renal cell carcinoma and mesothelioma. A total of 106 specimens have been sent for study. In addition, 14 peripheral blood and fibroblast specimens from members of cancer families have been examined for cytogenetic defects, as specified in the contract. The recent work has identified a subtype of renal carcinoma with a papillary histology, indolent clinical course and characteristic tetrasomy 7, trisomy 17 and -Y. Analyses of sarcomas has revealed an unusual osteosarcoma from a cancer family in which the only change appears to be a 13q14 deletion; possibility of deletion of the retinoblastoma gene is now under study. Also, an uterine stromal sarcoma with an unusual insertion [ins(10;19)] was found, as well as an undifferentiated sarcoma with a large HSR (homogeneously staining region) in chromosome 8 which might indicate amplification of an oncogene. Among karyotyped non-tumor tissue, a reported "radioresistant" fibroblast line from a member of a kindred with breast cancer-sarcoma syndrome showed aneuploidy, raising the possibility that the unusual response to radiation might be a tissue-culture artifact. This finding has led to re-biopsy of the case to establish new lines for study.

REGENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES (N01-CP-71081)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay A-Assays of Protein Polymorphisms).

Current Annual Level: $56,355

Person Years: .35

Objectives: To provide red blood cell, serum and plasma typings for a panel of 30 polymorphic genetic markers for use in genetic linkage studies.

Major Contributions: This year the laboratory has received and processed blood and serum specimens from 255 individuals in 14 families representing eight different hereditary disorders. The results of these studies have contributed to the mapping of the genes for multiple endocrine neoplasia type 1, hypertrophic cardiomyopathy and hereditary cutaneous malignant melanoma.

INTEGRATED GENETICS, INC. (N01-CP-71127)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay B-Assays of DNA Polymorphisms).

Current Annual Level: $378,122

Person Years: 4.1

Objectives: To provide DNA polymorphism typings on samples submitted for use in genetic linkage studies.

Major Contributions: The lab has thus far performed 390 assays on 78 persons with multiple endocrine neoplasia type 1 (MEN1) and another 468 assays are in progress. The information from this study has contributed to the mapping of the gene for MEN1. In an effort to locate the gene for the Li-Fraumeni syndrome, a further 480 assays of paired tumor/constitutive DNAs are in progress.

DEPARTMENT OF ENERGY, BROOKHAVEN NATIONAL LABORATORY (Y01-CP-20518)

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

Current Annual Level: $310,950

Person Years: 3.2

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 underlying cellular mechanisms.

Major Contributions: New fibroblast strains sent to the laboratory in the past year have been from Israeli immigrants irradiated in childhood for ringworm of the scalp. The strains consist of two groups: those from persons who developed cancer (usually of the thyroid or brain) following radiation exposure, and those from persons who did not. These strains have been the major focus of the laboratory's recent work.

In order to evaluate possible differences in response to ionizing radiation of the Israeli strains, the laboratory has been trying to develop a method that will distinguish among the cell growth characteristics of strains from normal individuals, persons homozygous for ataxia-telangiectasia (AT), and persons who are heterozygous for AT. This is necessary because we have postulated that the Israelis who developed tumors as a result of the radiation exposure may in fact be AT heterozygotes (the AT gene is known to be present in high frequency in the North African population from which the Israeli immigrants came) and possibly have an increased predisposition to radiogenic malignancies as a result. AT is an autosomal recessive condition which predisposes to lymphoproliferative malignancies and, both in vivo and in vitro, has abnormal sensitivity to ionizing radiation. In vitro, the D_{10} values for ionizing radiation of AT homozygotes are significantly lower than for controls, so that the two groups can be distinguished. Although some scientists have reported that the D_{10} values of strains from AT heterozygotes are intermediate between those of the AT homozygotes and normal individuals, this has not been generally confirmed.

To date, the Brookhaven laboratory has used a variety of different methods to see if any will consistently differentiate AT heterozygotes from normal individuals: these have included x-ray treatment of exponentially growing cells, x-ray treatment of confluent cell cultures, treatment of cell cultures with chronic doses of x-rays and treatment with neocarzinostatin, a radiomimetic chemical. Although none of these approaches can consistently distinguish AT heterozygotes from normal individuals, the laboratory has made parallel studies with the Israeli strains, in case some differences appear among them.

The method currently being evaluated (the Cumulative Labelling Index) involves irradiating cells in stationary growth, subculturing them in H^3-containing medium and then observing the number of cells that begin to divide as measured by the incorporation of the H^3 into DNA. For unknown reasons, the fraction of cells in which the x-ray treatment permanently blocks growth is much higher in AT heterozygotes than in controls. The Brookhaven laboratory has been able to replicate these results. The Israeli strains have also been studied using this method, but we will not break the code to determine the tumor status of the donors of these strains until replicate experiments have been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04400-24 CEB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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:	F.P. Li	Chief, Clinical Studies	CEB	NCI
Others:	R.W. Miller	Chief	CEB	NCI
	J.J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
	P.A. Siraganian	IRTA Fellow	CEB	NCI
	D.M. Parry	Geneticist	CEB	NCI
	J.E. Garber	Research Fellow	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 and through clinical observations at the bedside. With informed consent, epidemiologic inquiries are made to identify predisposing host and environmental factors, and to quantify the risk of cancer development. Concurrent laboratory studies are made to clarify biologic mechanisms of cancer susceptibility. Results show that carriers of cancer genes develop cancer at high rates in specific tissues, including multiple primary cancers in childhood. Work is in progress to map several of these recessive oncogenes, including genes for renal carcinoma, familial Wilms' tumor, and the dominantly inherited syndrome of breast cancer, sarcomas and other childhood neoplasms. 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 2000 survivors of childhood retinoblastoma in New York and Boston are being examined for the role of inherited susceptibility and ionizing radiation therapy in the development of second cancers.

Project Description

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

F.P. Li	Chief, Clinical Studies	CEB	NCI
R.W. Miller	Chief	CEB	NCI
J.J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
P.A. Siraganian	IRTA Fellow	CEB	NCI
D.M. Parry	Geneticist	CEB	NCI
J.E. Garber	Research Fellow	CEB	NCI

Objectives:

To employ clinical observation at the bedside to find causes of human cancers. Susceptibility factors in the development of cancer are identified, and laboratory studies made to uncover biologic mechanisms of predisposition to cancer. In addition, survivors of childhood cancer are followed for clues to the origins of their cancer that may not be evident until later life.

Methods Employed:

Patients admitted for cancer therapy at the Dana-Farber Cancer Institute are examined for clues to etiology of the neoplasm. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. In recent years, several striking family aggregates of specific cancers have been identified. Members of these kindreds are under study to identify reasons for the susceptibility and to detect early cancers. 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. In addition, registries have been established of more than 1,000 patients who have survived childhood cancer at Dana-Farber Cancer Institute, and 2,000 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.

Major Findings:

Hereditary Renal Cell Carcinoma

Additional studies have been made of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Somatic cell hybrids with the derivative chromosomes show that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3 and that the RFLP, D3S2, is rearranged to the derivative 8. However, pulse field gel electrophoresis recently

showed that c-myc is not within 700 Kb of the breakpoint. Studies of chromosome 3 by several groups have shown chromosome 3p rearrangements in renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. Our studies revealed that chromosomes 3 and 5 are commonly involved in renal carcinoma, but that a rare subtype of this cancer has different alterations. Several techniques are now being used to further localize the breakpoint on chromosome 3 in our family. The hypothesis is that the gene on 3p that is involved in the development of human renal carcinoma is at the breakpoint of the t(3;8) in our family, and that it is not the von Hippel-Lindau's gene on distal chromosome 3p.

The Familial Breast Cancer-Sarcoma Syndrome

An analysis of 24 families has clarified the clinical features of this syndrome: sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. A prospective follow-up study is nearing completion on the occurrences of new cancers among family members since initial ascertainment of the kindred. The data show that approximately 30 percent of cancer survivors in the family have developed second neoplasms on follow-up observation. Investigations are in progress of 13 additional families that appear to have the syndrome. Cytogenetic studies of soft tissue sarcomas from familial and sporadic cases show correlations between chromosomal translocation and histological subtype of the sarcoma. These include the translocation, t(X;18), in synovial sarcoma, deletion of chromosome 11p in rhabdomyosarcoma and translocation between chromosomes 12 and 16 in liposarcoma. The findings may be useful in classifying poorly differentiated soft tissue sarcomas, and to localize genes involved in the development of sarcomas. In addition, work is in progress to clone the X;18 translocation breakpoint in synovial sarcoma.

Mapping the Gene(s) for Familial Wilms' Tumor

Studies of the association of Wilms' tumor with aniridia or with hemihypertrophy have led to a search for Wilms' tumor genes on the short arm of chromosome 11. The rarity of Wilms' tumor in families have precluded informative linkage analyses. In our previously reported family with Wilms' tumor in 5 children, follow-up observation has revealed 2 additional cases with the neoplasm. Linkage analysis of this and other available families has excluded chromosome 11p as the locus of the "familial Wilms' tumor gene," and a search for its true location will be initiated.

Mesothelioma in Cigarette Filter Makers

We recently observed mesothelioma in 3 men who had made cigarette filters which contain asbestos. All had worked for one small company between 1951 and 1958. According to the patent, the cigarette filter contains 5 to 30 percent blue asbestos, or crocidolite. An additional 33 workers at this plant have been identified and our follow-up has revealed 5 deaths from mesothelioma, 7 from lung cancers, and 5 from asbestosis.

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, we have found 4 families in which a child has developed hepatoblastoma, a newly described association. We then surveyed known polyposis registries, and found 11 additional examples of the association. We have established a Registry of the Hepatoblastoma-Polyposis Coli Association and have begun collection of specimens for laboratory studies.

We have recently observed 5 cases of multiple primary cancers that include melanoma and soft tissue sarcoma. Two of them also have dysplastic nevus syndrome (DNS). The possibility that sarcomas are a previously unrecognized feature of DNS is under study.

Late Effects in Survivors of Childhood Cancer

A number of studies have been undertaken to evaluate adverse effects of late onset among childhood cancer survivors. In a 14-year follow-up of patients previously studied for the occurrence of second cancers at the Dana-Farber Cancer Institute, 23 new cancers were observed when 2 were expected. All but 2 of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The findings indicate that the high risk of second neoplasms among childhood cancer survivors extend far into adult life.

A seven-hospital study has shown that women treated in childhood for Wilms' tumor with radiotherapy had a high frequency of adverse pregnancy outcome, particularly delivery of low-weight infants. To pursue this unexpected observation, a new series is being gathered of offspring of patients who had radiation for childhood cancers other than Wilms' tumor. Preliminary data suggest that low birthweight also occurs among offspring of these irradiated female patients.

A recent study reported a 90% risk of second cancers, primarily sarcomas, among nearly 800 survivors of hereditary retinoblastoma. However, the risk estimate may be flawed by a high proportion of cases lost to follow-up. To refine the risk, a follow-up study of these cases and 1,200 others with retinoblastoma is in progress. The study has provided access to tissue of second cancer in retinoblastoma patients. These tissues are being probed for loss of the retinoblastoma gene.

The frequency of hypertension has been studied in a series of Wilms' tumor patients who had nephrectomy and other treatments between 14 and 53 years ago. Eighty percent are normotensive. The overall frequency of hypertension did not exceed expectation based on data for the general population. The data provide assurance that hypertension is not a common sequelae of treatment for Wilms' tumor. We now plan to study renal function in those patients who had nephrectomy and abdominal radiotherapy in childhood.

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. Specimens collected from these patients have created opportunities to collaborate with laboratory scientists in studies of the pathogenesis of human neoplasia, with particular attention to the role of recessive oncogenes. In the past year, Dr. Judy Garber has continued to work in the Section as an Epidemiology Research Fellow, and Dr. Arlene Kantor has transferred to the Section from the Environmental Epidemiology Branch. In recent years, research based upon our observational research have attracted students, physicians in training and other health professionals to work with us. Currently these include Drs. Jim Talcott and Fred Kass, medical oncology fellows at the Dana-Farber Cancer Institute.

Hereditary Renal Cancers in Children and Adults

Studies of the association of Wilms' tumor with aniridia or with hemihypertrophy have led to a search for Wilms' tumor genes on the short arm of chromosome 11. We have recently reported in Nature that a linkage analysis of a family with 7 children having Wilms' tumor has excluded chromosome 11p as the locus of a "familial Wilms' tumor gene," and a search for this locus has been initiated. In addition, studies of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8 have shown that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3, but that c-myc is not within 700 Kb of the breakpoint. Studies of chromosome 3 by us and others have shown chromosome 3p rearrangements in renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. Several techniques are now being used to clone the breakpoint on chromosome 3 in our family.

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Several new studies have been made on this syndrome, originally described in 4 families by Li and Fraumeni. Recent analysis of 24 affected families has clarified the clinical features of this syndrome: sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. A prospective study of new cancers among family members since initial ascertainment shows that approximately 30 percent of cancer survivors in the family have developed second neoplasms on follow-up observation. Investigations are in progress of 13 additional families that appear to have the syndrome. Cytogenetic studies of soft tissue sarcomas showing correlations between chromosomal translocation and histological subtype of the sarcoma are being pursued in work in progress to clone the X;18 translocation in synovial sarcoma.

Mesothelioma in Cigarette Filter Makers

Clinical observations can identify cancer clusters due to potent environmental carcinogens. We recently observed mesothelioma in 3 men who had made cigarette filters which contain asbestos, particularly highly

carcinogenic blue asbestos, or crocidolite. An additional 33 workers at this plant have been identified and on follow-up 5 deaths from mesothelioma, 7 from lung cancers, and 5 from asbestosis were found.

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We have recently observed 5 cases of multiple primary cancers that include melanoma and soft tissue sarcoma. Two of them also have dysplastic nevus syndrome (DNS). Dr. Garber is examining the possibility that sarcomas are a previously unrecognized feature of dysplastic nevus syndrome.

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Publications:

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Parry DM, Mulvihill JJ, Miller RW, Berg K, Carter CC. Strategies for controlling cancer through genetics. Cancer Res 1987;47:6814-7.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05139-10 CEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

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

COOPERATING UNITS *(if any)*
CC (S. Schlesinger); NEI (M. Kaiser-Kupfer); NIDDK (B. White); NICHD (W. Gahl, J. Sidbury); NINDS (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 236 individuals representing some 60 different diagnostic categories. Of these, 84 patients 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 benign or malignant tumors. 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, 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 Section	CEB	NCI
C. A. Collins	Research Assistant	CEB	NCI

Objectives:

1. To provide a multidisciplinary setting in which patients with cancer or at high risk of developing 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

Neurofibromatosis type 2	30
Neurofibromatosis type 1	21
Hypereosinophila syndrome	5
Women at high risk of breast cancer	4
Nevoid basal cell carcinoma syndrome	3
von Hippel-Lindau's disease	3
Familial leukemia	2
Other familial cancers	5

Lymphedema with lymphangiosarcoma	1
Pancreatic cancer	1
Sarcoma	1
Squamous cell carcinoma	1
Tuberous sclerosis	1
Ruvalcaba-Myrhe-Smith's syndrome	1
Birth defect syndromes or cytogenetic abnormalities	5
TOTAL	84

Major Findings:

As in the past, we continue to be interested in clarifying the genetics and natural history of the neurofibromatoses. In view of the fact that neurofibromatosis type 1 (NF1) has been mapped to a band in the long arm of chromosome 17, the result of an international scientific collaboration in which Drs. Parry and Mulvihill were very active participants, much of our research effort is now focused on bilateral acoustic neurofibromatosis, known as NF2. This disorder causes development of schwannomas of the vestibular nerve, usually resulting in bilateral hearing loss in adolescent or early adult life. Surgical removal of these tumors presents formidable difficulties because of the risk of facial and auditory nerve damage. This condition is also associated with a high incidence of meningiomas, gliomas and neurofibromas of the spinal nerve roots. Over the last two years, we have evaluated a total of 25 patients with NF2, including 19 from five multigeneration families and 25 of their first degree relatives with a battery of examinations, that in addition to a physical examination, include: magnetic resonance imaging of the brain with gadolinium, ophthalmoscopy, audiometry and auditory brainstem-evoked responses. Results of the ophthalmic studies on many of our patients confirmed the association, first documented at NIH, between acoustic neuromas and the development of the presenile posterior capsule lens opacities. We have now seen congenital cortical cataracts in several NF2 patients which may be another manifestation of this pleiotropic gene.

We plan to pursue two types of studies of NF2. The initial goals of the first study will be to evaluate clinical heterogeneity and the effect of gender on prognosis. We are hypothesizing three subtypes of NF2:

1. families with bilateral acoustic neuromas and cataracts;
2. families with bilateral acoustic neuromas, multiple meningiomas and spinal neurofibromas in addition to cataracts; and
3. families with bilateral acoustic neuromas, meningiomas, ependymomas but no cataracts.

We will use new clinical data to assess the validity of these subtypes. Further, by analyzing the clinical data by sex, we will determine whether women with NF2 have an earlier age at onset of symptoms and an increased frequency of associated brain and spinal cord tumors than affected men, as our current data seem to suggest.

The initial goal of the second type of studies is to evaluate genetic heterogeneity in NF2. DNA studies of acoustic neuromas, meningiomas and neurofibromas from NF2 patients and from blood from one large three-generation NF2 family support the existence of a gene for NF2 on chromosome 22. However, the studied family was atypical, lacking the cataracts seen in about 90% of our patients. Therefore, we are conducting genetic linkage studies with chromosome 22 RFLPs in our three largest NF2 kindreds. If chromosome 22 linkage is confirmed, these and other families will be used to fine map NF2. If NF2 in our families does not map to 22, we will assay the families' DNA with random DNA probes. The results of the DNA studies will be the ultimate judge of the clinical heterogeneity that we have hypothesized.

In addition to the linkage studies, tumor DNA from our patients will be examined to identify interstitial deletions that may precisely map the NF2 gene.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05146-10 CEB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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
	R. R. Connelly	Statistician	BB	DCPC	NCI
	M. H. Gail	Head, Epidemiologic Methods	BB	E&BP	NCI

COOPERATING UNITS *(if any)*

NICHD (R. Sherins):

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. Marriage deficits were significant among men and women who had been treated for brain tumors. The first marriages of men who had survived brain tumors and of men who had survived retinoblastoma were likely to break up than those of controls. Survivors of childhood brain tumors were also less likely to complete 8th grade, or to enter college after high school graduation. Overall, survivors were less likely to acknowledge that they had had cancer, especially if they were non-white, had been diagnosed in Connecticut, or had been treated in earlier years.

A registry of pregnancies exposed to cancer treatments has been in place for some years, and continues to accrue cases. The Proceedings of an International Conference on Reproduction and Human Cancer are in preparation. Follow-up studies of former leukemia patients are underway, with collaboration from the Childrens Cancer Study Group and the National Institute of Child Health and Human Development.

Project Description

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

J. J. Mulvihill	Chief, Clinical Genetics Sect.	CEB	NCI
J. M. Byrne	Epidemiologist	CEB	NCI
R. R. Connelly	Statistician	BB, DCPC	NCI
M. H. Gail	Head, Epidemiologic Methods Sect.	BB, E&BP	NCI
D. M. Parry	Geneticist	CEB	NCI
E. Mostow	Staff Fellow	CCAB	NCI
R. Haupt	Visiting Scientist	CEB	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. Marriage rates in our survivors were significantly less than in controls; males had a 30% marriage deficit compared to male controls, while females were not different from female controls in their marriage rates. Most of the male marriage deficit occurred to survivors of brain and central nervous tumors, who were 30% less likely than their controls to marry. Income deficits were also seen in male cancer survivors, again among brain tumor survivors principally. We speculate that the same cognitive and functional problems attendant upon treatment for brain tumors which lead to income deficits also make them poor marriage prospects.

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. In collaboration with Dr. Mitchell Gail of the Biostatistics Branch, we are investigating the rates of menopause in female survivors compared to female controls. At the time of interview, 22% of survivors were post-menopausal compared to 15% controls. The average age at menopause for survivors was 25 versus 35 for controls. All cancer treatments were associated with early menopause in the period shortly after the start of therapy, but only two--radiation below the diaphragm alone and radiation below the diaphragm plus alkylating agent chemotherapy--were associated with effects lasting more than 10 years since the start of treatment.

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 completed 8 years of school or to have entered college.

Data from the Five-Center Study confirm a previous report 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. These women also have more children with birth defects than female controls. Male survivors reported no such problems in their wives.

After noticing that 22% 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, who came from Connecticut 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."

We analyzed rates of birth defects in offspring of survivors compared to offspring of controls. Using various sources of ascertainment--parents' reporting, cancer registry records and other medical records--no association between parents' history of cancer and offsprings' birth defects could be detected. When we looked at the subgroup of survivors exposed to mutagenic or teratogenic therapy, compared to offspring of survivors not so exposed, there was no excess of birth defects.

In our analyses to date we have not detected any evidence that potentially mutagenic cancer therapy is actually linked to genetic effects in the offspring. Other endpoints (e.g., sex ratio and fetal loss) are being studied.

Other Collaborations:

Through a collaborative arrangement with the Children's Cancer Study Group, we are exploring the possibility of studying various aspects--late effects of leukemia and its treatment in long-term survivors. We plan to do an interview study of survivors over 18, similar to the Five-Center Study, to

examine the health and fertility of survivors and the health of their offspring. Two prospective clinical studies of growth and development are planned in collaboration with endocrinologists from the National Institute of Child Health and Human Development and New York University. We plan to obtain tissue samples prospectively to look for precursors of future cancer development in these high risk children.

Plans are well underway for a follow-up study of cancer survivors treated at the NIH Clinical Center and their offspring conceived since treatment. The goal is to study at least three members of a family--the exposed survivors, the unexposed spouse and the offspring--for the possible mutagenic effects of treatment, manifested as mutant problems which may or may not have clinical significance.

Through a contractual arrangement set up by the Viral Epidemiology Section of NCI's Environmental Epidemiology Branch, we are collaborating with Dr. Janet Neequaye of the University of Ghana Medical School to study the fertility of long-term survivors of African Burkitt's lymphoma. Data collection has concluded, and we expect that analysis will commence in the summer of 1989.

Publications:

Byrne J. The impact of selected psychosocial factors on the reproductive choices of long-term survivors of childhood and adolescent cancer. In: Mulvihill JJ, Sherins R. eds. Reproduction and human cancer. New York: Raven Press. (In Press)

Byrne J, Mulvihill JJ, Connelly RC, Myers MH, Austin DF, Holmes GF, Holmes FF, Latourette HB, Meigs JW, Strong LC. Reproductive problems and birth defects in survivors of Wilms' tumor and their relatives. Med Pediatr Oncol 1988;16:233-40.

Kelaghan J, Myers MH, Mulvhill JJ, Byrne J, Connelly RR, Steinhorn SC, et al. Educational achievement of long-time survivors of childhood and adolescent cancer. Med Pediatr Oncol 1988;16:320-6.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05194-08 CEB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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 personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.W. Miller	Chief	CEB	NCI
Others:	F.W. McKay	Computer Systems Analyst	CEB	NCI
	P. Madigan	Health Statistician	CEB	NCI
	J.M. Byrne	Epidemiologist	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.)*

The Branch created a data file from death-certificate diagnoses for the 8 million people who died of cancer in the U.S. from 1950 through 1982. Three-dimensional graphs employing these data are one example of the value of the data collection. Volumes on mortality data according to the state of residence, county, and State Economic Areas have been published. Now Surveillance, Epidemiology and End Results (SEER) program data are being used for incidence studies of special population groups and subclassifications of cancers. Experimentation with mapping U.S. cancer mortality by economic subareas that cross state lines revealed some hot-spots not apparent by use of the traditional State Economic Areas (SEAs), which do not cross state boundaries.

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
P. Madigan	Health Statistician	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:

1. Cancer mortality data collected by the National Center for Health Statistics (NCHS) for 1950-1982 are assembled in a data base. These are accessible by 4-digit International Classification of Diseases code and 18 age groups at the county level. Three-dimensional graphs of cancer mortality rates by site, sex, calendar year and age group for whites and non-whites can be made.

2. For mapping mortality data, we made use of economic subregions (ESRs, N=119) as defined by Bogue and Beale of the Bureau of the Census in 1961, and the Bureau of Economic Analysis (BEA) areas (N=183), neither of which is confined by State boundaries. Counties are aggregated with respect to economic similarities.

3. Standardized mortality ratios (SMRs) for nasopharyngeal cancer deaths in Florida from 1953-82 were mapped with respect to county, SEA, ESR and BEA areas.

4. Case-control study of hot spots revealed by mortality studies by BEAs may identify environmental carcinogens in these areas.

5. A study will be made of correlations among cancers by geographic area.

Major Findings:

1. An excess of nasopharyngeal cancers among U.S. white males, 1950-1975, was found along the Gulf Coast using ESRs.

2. For SMR maps of nasopharyngeal cancer in Florida, regions with significantly high SMRs varied according to the economic grouping used (i.e. BEA, SEA, county, ESR). Combining a high-rate county with various groups of its neighbors washed out the high SMR in some instances.

3. Using BEAs, among the notable clusters are high SMRs for stomach cancer in the BEAs for Duluth, MN; Providence, RI; Wausau, WI; and Albuquerque, NM. In Duluth, 313 males died of stomach cancer as compared with 193 expected from 1970-1980.

4. From 1979-1982, a cluster of 13 cases of Burkitt's lymphoma occurred among males in the BEA for Minneapolis-St. Paul. More recent data are needed, and a case-control study may point to a cause. In 1968-1982, high rates for cancer of the pleura (probably mesothelioma) were noted in males in the BEAs for Seattle; Buffalo; Rochester; Huntington, WV; and Norfolk, and for males and females in the area of Harrisburg, PA. Studies of the environmental exposures of these decedents may reveal previously unrecognized carcinogenic hazards, which can be prevented in the future.

5. One-third (6 of 18) of the BEA areas with highest rates for cancer of the lip also had the highest rates for cancer of the salivary gland. Waco, TX and Lexington, KY had not only high rates, but also a ratio of 1:1 for these cancers instead of two salivary for each lip cancer. The deaths generally were 40+ years of age. Further study may reveal the basis, if any, for the association between lip and salivary gland mortality in these areas.

6. The highest rates for cancer of the gall bladder were in areas with large Hispanic populations, a group known to be at higher risk than other ethnic groups. Of the 18 areas with the highest rates, eight were high for both males and females, 1970-1980. Among the eight, those that did not have large Hispanic populations were Duluth; Eau Claire, WI; Minot, ND; Fargot, ND; and Erie, PA.

7. Mortality from cancer of the uterine cervix should be preventable through early detection and treatment. The national age-adjusted rate, 1970-1980, for U.S. whites was 6.5 deaths per million. In Brownsville, TX the rate was 12.0; in Terre Haute, IN, 11.6; in Huntington, WV, 11.6; and in Charleston, WV, 11.1. Efforts toward prevention should be concentrated in these areas.

8. A high proportion of cancer of the urinary bladder is environmentally induced. Areas that showed the highest mortality rates among males included Providence, RI (16.3 per million); Burlington, VT (15.2); and Buffalo, NY (15.2). The national age-adjusted rate was 11.6 per million.

9. Finally, as previously shown by others, the northeast has the highest total cancer mortality in the country. The cancers responsible are mainly of the gastrointestinal tract, urinary bladder, lung and larynx; but surprisingly, in four of the eight areas, the mortality rates for Hodgkin's disease in one or both sexes were in the top decile. A study will be made of the correlations among these cancers.

Publications:

Croner CM, McKay FW, Jr. Changing geographies of cancer mortality maps. In: ACSM-ASPRS Falls Church VA Convention. ACSM Technical Papers. Virginia Beach: American Congress on Surveying and Mapping, 1988;206-16.

Miller RW. Epidemiologic evidence for genetic variability in the frequency of cancer: ethnic differences. In: Woodhead, AD, Bender, MA, Leonard, RC, eds. Phenotypic variation in populations. New York: Plenum Press, 1988;65-70.

Miller RW. The frequency of cancer in the very young. In: van Eys J, ed. Cancer in the very young. Springfield, IL: C C Thomas. (In Press).

Miller RW. Geographical and ethnic differences in the occurrence of childhood cancer. In: Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. International incidence of childhood cancer. IARC Sci Publ 1988;87:3-7.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05279-06 CEB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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

Development of Epidemiologic Data Resource

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:	A.E. Blair	Epidemiologist	EEB	NCI
	J.D. Boice	Chief	REB, EBP	NCI
	B.F. Hankey	Biostatistician	DCPC	NCI
	Z. Hrubec	Expert	REB, EBP	NCI
	R.H. Hoover	Chief	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 facilitate the development of data resources for cancer epidemiology, a working group was established by the Director, NCI, in 1978. The membership includes those named above, with Dr. Beebe as chairman. The present functions of the group include creating a national data base for occupational mortality, reviewing Master Order Agreement-Requests for Proposals, oversight of the Veterans Administration (VA) hospital discharge file, liaison with the National Center for Health Statistics in regard to the National Death Index, improving access to Federal record systems, and pursuing new leads. A number of contracts or interagency agreements have been initiated in support of this program, especially with the Social Security Administration (SSA) and the Internal Revenue Service (IRS). A legislative initiative has been drafted in the Office of the Assistant Secretary for Health to widen the access of medical investigators to the address file of the IRS.

Project Description

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

G.W. Beebe	Health Statistician	CEB	NCI
A.E. Blair	Epidemiologist	EEB	NCI
J.D. Boice	Chief	REB, EBP	NCI
B.F. Hankey	Biostatistician	DCPC	NCI
Z. Hrubec	Expert	REB, EBP	NCI
R.H. Hoover	Chief	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.

3. To oversee exploitation of the VA hospital discharge file.

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. The Social Security Administration (SSA) has now been persuaded to join the Health Care Financing Administration in its willingness to provide addresses and social security numbers for occupational studies performed by investigators in the Department of Health and Human Services. Efforts continue to amend the legislation that limits access to IRS addresses for studies of occupational factors in disease.

2. A comparison of information in SSA files with that obtained after death and from next-of-kin has been attempted, to test for completeness and reliability on the part of next-of-kin reporting of occupational histories. SSA file arrangements made the necessary searches far too expensive for most studies. The pilot project to explore the agreement between the two sources of employment information is nearing completion.

3. For study of mortality in relation to occupation and industry, several efforts have been mounted to explore the possibility of creating a national system for surveillance and hypothesis-generation. NCI has joined the National Institute for Occupational Safety and Health (NIOSH) in funding a program under which states are encouraged to perform industry and occupation Industry and Occupation coding in a standard way and the National Center for Health Statistics (NCHS) performs a quality-control function as well as collating the material for analysis. For 1986 the files of 18 states are available, comprised of 517,000 records.

4. Under an interagency agreement with NCI, IRS has shown that it can code occupation from IRS Form 1040, provided it has industry information from SSA. IRS is currently processing a file of about 260,000 taxpayers in 1979 with 18,000 deaths in an effort to learn whether the addition of its information on occupation to that of SSA on industry would provide insight into cause-specific mortality beyond that obtainable from tabulations confined to industry.

5. The SSA Continuous Work History Sample (CWHS) is a one percent sample of SSA registrants. Under an interagency agreement wth NCI, SSA has obtained death certificates for about 90,000 deaths in the CWHS during the 1973-77 interval. Cause of death has been obtained from NCHS and Industry and Occupation coding of death certificates has been done by Census. The plan is to test the file by seeking well-known cause-specific mortality differentials by industry of employment. One feature of the CWHS is its historical information on industry of employment starting in 1957. At present the file is being studied for useful ways of patterning these histories.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05280-06 CEB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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:	R.W. Miller	Chief, Clinical Epidemiology Branch		NCI
	C.E. Land	Statistician	EEB	NCI
	J.D. Boice	Chief, Radiation Epidemiology Branch		NCI
	B.W. Wachholz	Chief, Radiation Effects Branch		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 study of thyroid nodules was conducted among older women in an area of high background radiation in China. No excess was found. Dr. Beebe served as Assistant Project Officer for the study. A study of skin fibroblast sensitivity in vitro was made of women with breast cancer vs. other women, atomic-bomb exposed vs. unexposed. The study showed no difference in cell-killing by acute radiation exposure.

Staff experience since the 1950s in writing and advising on the effects of ionizing and other forms of radiation on human health is often drawn upon. Dr. Beebe has long been associated with study of Japanese A-bomb survivors. He contributes to program planning by making specific research suggestions, reviewing research protocols, and recommending research strategy. He participated in the 1988 RERF workshop on sensitivity to the effects of ionizing radiation on man and the 1989 RERF workshop on radiation carcinogenesis. Dr. Miller has provided consultation to the Departments of Energy, Justice, and Labor, and the National Council on Radiation Protection and Measurement.

Project Description

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

G.W. Beebe	Statistician (Health)	CEB	NCI
R.W. Miller	Chief, Clinical Epidemiology Branch		NCI
C.E. Land	Statistician	REB	NCI
J.D. Boice	Chief, Radiation Epidemiology Branch		NCI
B.W. Wachholz	Chief, Radiation Effects Branch		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. Investigators continue to examine their data to infer the lowest dose responsible for a carcinogenic effect. In a study of thyroid nodules in older Chinese women living in a high-background area, there was essentially no evidence that nodular thyroid disease was elevated among residents.

2. Review papers have been written on human health effects of ionizing radiation and on Atomic Bomb Casualty Commission (ABCC) and Radiation Effects Research Foundation (RERF) findings. Reports on the intrauterine effects of exposure to ionizing radiation, stressing the importance of small head size at very low doses have been published.

3. Dr. Beebe's interest in planning for scientific exploitation of research opportunities offered by radiation disasters has led the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) to establish a subpanel to consider this subject. Issues considered by the Panel are compensation, effects of non-ionizing radiation, radon, and many other topics.

Publications:

Beebe GW. Cancer in atomic bomb survivors. In: Accomplishments in Cancer Research. General Motors Cancer Research Foundation, Philadelphia, Lippincott. (In Press).

Beebe GW. Carcinogenic effects of nuclear radiation. J Wash Acad Sci 1988;78:101-16.

Beebe GW. Studies of cancer among the Japanese A-bomb survivors. Cancer Invest 1988;6:417-26.

Miller RW. Intrauterine radiation exposures and mental retardation. Health Phys 1988;55:295-8.

Upton AC, Albert RE, Barrett JC, Beebe GW, Nebert DW, Ray AV, Rice R, Wilson R, Yuspa S. Report of the NCRP Task Group on the comparative carcinogenicity of ionizing radiation and chemicals. Bethesda, National Council of Radiation Protection and Measurements. NCRP Report #96, 1989;179

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05329-06 CEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Hepatitis B Virus (HBV) 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:	G.W. Beebe	Statistician (Health)	CEB	NCI
Others:	C.E. Land	Statistician	EEB	NCI
	J.D. Boice	Chief, Radiation Epidemiology Branch		NCI
	B.W. Wachholz	Chief, Radiation Effects Branch		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, NIDDK, (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	0.3	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.)

A serologic study was completed and published in the New England Journal of Medicine in 1987. Three groups were defined: I, men hospitalized in 1942 with post-vaccinal hepatitis; II, men vaccinated from contaminated lots of vaccine who did not become ill; and III, men who entered the Army only after the vaccine was withdrawn. The serologic examination of 597 men showed that the 1942 epidemic was caused by HBV. A cohort mortality study of about 60,000 men representing the same three groups is essentially finished and a manuscript is in preparation. Mortality from all causes was quite similar in the three groups, standardized mortality ratios (SMRs) being .89, .87, and .88 for Groups I, II, and III, respectively. For all malignant neoplasms the parallel SMRs differed significantly, being .87, .77, and .85 in the same sequence. Deaths from cirrhosis were comparable for the three groups. There were 65 deaths coded to 155.0 (primary hepatocellular carcinoma [PHC]) and 155.2 (liver cancer, not specified as primary or secondary). The three groups did not differ significantly with respect to these causes as coded from the death certificates. From a blind review of all available pathology material, a small excess of definite PHC deaths emerged that seems inconsistent, in its size, with generally held views of the likelihood that HBV infection will generate the carrier state and the likelihood that a carrier will develop PHC. Although other interpretations may be possible, the results of the cohort study strongly suggest that the relationship between PHC and HBV infection depends on age at infection. Adults infected with HBV appear to have low carrier rates and perhaps also low transition probabilities from the carrier state to PHC.

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	EEB	NCI
J.D. Boice	Chief, Radiation Epidemiology Branch		NCI
B.W. Wachholz	Chief, Radiation Effects Branch		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 has been 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 a sample cleared against the National Death Index to check on VA records. Death certificate diagnoses of liver cancer and other liver diseases have been investigated through hospital records and available

pathology material to refine the comparisons as to risk of death from PHC. Comparison of the three cohorts has been performed both directly in age-adjusted fashion and by means of standard mortality ratio calculations.

Because the definition of Group II is somewhat indirect, a case-control study is being performed on the basis of VA hospital discharges for PHC. The case-control study will yield more certain evidence of vaccine lot number than the cohort study, and it was hoped that there would be many more evidential immunization registers in the case-control study than deaths from PHC 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.

VA hospital cases of liver cancer in WWII Army veterans and matched controls have been traced through military records files in St. Louis for evidence of yellow fever vaccine lot number to permit a comparison to be made as to the frequency of contaminated lots in each group. The comparison is restricted to cases (and their controls) of PHC only.

The serum for the Rockefeller vaccine was obtained from bleedings at Johns Hopkins Hospital in 1941-1942. The Johns Hopkins donor book has been obtained, together with all correspondence and questionnaires that figured in the epidemiological investigation by the Army and the Rockefeller Foundation in 1942-43. Since blood was drawn from students and staff, and serum lots are tied to the vaccine lots, it may be possible, even now, to bleed some donors who contributed to the serum pools used to create the contaminated lots. There are some ethical considerations under study, but an effort was made in 1942-43 to inform all donors of the epidemic and its connection with the vaccine.

Because the documentation of the epidemic makes it possible to separate acute cases of clinical hepatitis, and therefore presumably transient infections, from subclinical and potentially chronic infections, the 1942 material provides an opportunity to explore issues that relate to this distinction. The most important one concerns its significance for the carrier state and the likelihood of later liver cancer. Although the present survey does indicate that any excess risk of liver cancer from the 1942 infection is, at most, small, there is a unique set of veterans who were compensated by the Veterans Administration for residuals of hepatitis in 1957. This file is being explored for its possible usefulness in determining whether there was any excess risk of liver cancer, whether the excess risk was indexed by a chronic state in 1957, and whether the clinical and subclinical cases differ in this respect.

Major Findings:

1. A serologic study was completed and published in the New England Journal of Medicine in 1987. The serologic examination showed that the 1942 epidemic was caused by HBV.

2. A cohort mortality study of about 60,000 men representing the same three groups defined above is essentially finished and a manuscript is in

preparation. Mortality from all causes was similar in the three groups. For all malignant neoplasms the parallel SMRs differed significantly, being .87, .77, and .85 for Groups I, II, and III. The three groups did not differ significantly with respect to deaths coded to 155.0 (PHC) and 155.2 (liver cancer, not specified as primary or secondary) on death certificates.

From a blind review of all available pathology material, a small excess of definite PHC deaths emerged that seems inconsistent, in its size, with generally held views of the likelihood that HBV infection will generate the carrier state and the likelihood that a carrier will develop PHC. Although other interpretations may be possible, the results of the cohort study strongly suggest that the relationship between PHC and HBV infection depends on age at infection. Adults infected with HBV appear to have low carrier rates and perhaps also low transition probabilities from the carrier state to PHC.

3. Data collection for the case-control study has been completed and is being prepared for analysis. Quality of VA hospital diagnoses of PHC has been poor. It has been possible to verify diagnoses for less than half the cases in the VA diagnostic index of hospitalizations. Controls have been selected and matched on a 2:1 basis with regard to hospital, discharge date, year of birth, sex, and race. Statistical power will be much lower than anticipated in 1983.

ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

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.

One doctoral level and two master's level investigators left the Branch within the past year. Dr. Linda Pickle left the Population Studies Section for a position at Georgetown University's Comprehensive Cancer Center. Ms. Nancy Dalager left the Population Studies Section for a position in the epidemiology program of the Veteran's Administration, and Mr. Barry Miller left the Occupational Studies Section for a position within the Division of Cancer Prevention and Control of NCI. Two postdoctoral fellows also left; Dr. Kay Brock to a position at Columbia University and Dr. Carol Jones to a position with the Occupational Safety and Health Administration. Dr. Robert Biggar of the Viral Epidemiology Section spent the last nine months of the year as a Visiting Scientist at the Danish Cancer Registry in Copenhagen, Denmark. Dr. Linda Pottern transferred from the Biostatistics Branch to the Occupational Studies Section of the EEB, and Dr. Charles Rabkin was detailed from the Centers for Disease Control to the Viral Epidemiology Section to assist in investigations of malignancies related to retroviruses.

A number of young scientists joined the Branch within the past year in a variety of postdoctoral fellowship positions. These included Drs. Potischman, Chen, and Breman. In addition, four students participated in training opportunities through the Student Research Training Program, and Ms. Susan Sturgeon joined the Environmental Studies Section to work on her thesis project at Columbia University. The EEB also continues to provide a focus for training of a number of foreign scientists. In the past year, scientists from Greece, Italy, Costa Rica, Germany, China, Turkey, Sweden, and Brazil have all spent varied periods of time in the Branch, engaging in collaborative analysis of a number of data sets.

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.

A major effort in this program area has been the development of an updated Atlas of U.S. Cancer Mortality Among Non-Whites, with a focus on time trends in cancer mortality among non-whites over the 30-year period from 1950-1980. Perhaps the most striking finding from the effort is the marked tendency over this period for high rates from prostate cancer to cluster in counties in the southeastern U.S. In addition, utilizing data from a population-based tumor registry within a prepaid health plan, an in-depth evaluation of time trends in breast cancer was undertaken. Overall the incidence of this disease has risen 45% from 1960 to the mid-1980s, with the largest increases occurring among women over age 60. Localized and regional diseases have shown similar rates of increase. Availability of receptor assays since the mid-1970s indicates that estrogen receptor-negative cancers rose 25% between the mid-1970s and mid-1980s, while estrogen receptor-positive tumors have gone up an average of 131% during the same time period.

Field Studies in High-Risk Areas: The descriptive studies outlined above are constantly evaluated for observations that might be profitably followed-up with analytical field investigations in high-risk areas of the United States and the rest of the world. Activity in this program area over the past year has focused on studies of pancreatic cancer in southern Louisiana; laryngeal cancer along the Texas Gulf coast; and lung cancer in New Jersey. Internationally, case-control investigations of gestational trophoblastic disease in China, and cancer of the uterine cervix in Latin America were conducted because of the markedly elevated rates of these tumors in these particular areas.

In the pancreatic cancer study, analysis of a large number of dietary variables revealed evidence of excess risks associated with pork and rice consumption and a strong protective influence for fruit intake. Risk of laryngeal cancer in coastal Texas was related in a dose-response manner to number of cigarettes smoked daily, rising to 10-fold for smokers of two or more packs per day. Alcohol consumption was also related to excess risk, but only for supraglottic laryngeal cancer. Occupational determinants were also evaluated. Excess risks were noted for work in the transportation, metal manufacturing, construction and maintenance industries, as well as among those exposed to asbestos, paint and diesel/gasoline fumes. Analyses of the case-control study of invasive cervical cancer in four areas of Latin America have revealed a number of provocative associations. One of the most intriguing, which might help explain the very high rates of this disease in Latin America, is a progressively increasing risk with increase in number of pregnancies, rising to fourfold for a substantial number of women having had 10 or more pregnancies. This study also provided an opportunity to evaluate the hypothesized "male" factor. Among women claiming only one sexual partner there was an increased risk associated with increasing number of sexual partners by her husband.

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.

A number of investigations are underway to evaluate the risk of several different malignancies associated with the use of agricultural chemicals. A twofold excess risk of leukemia was noted among agricultural extension agents from the U.S. Department of Agriculture who came into contact with pesticides while conducting demonstration projects for farmers. In a separate investigation, an excess risk of non-Hodgkin's lymphoma was noted among soil and forest conservationists, a risk that rose to threefold for those so employed for 15 or more years.

Occupational risks of lung cancer were identified in two industries. Underground hematite miners had a fourfold excess risk, probably attributable to their exposures to silica and radon. Long-term workers in the chromium pigment industry were at a threefold excess risk of lung cancer. On the other hand, an exhaustive analysis of the excess risk of lung cancer previously noted in formaldehyde workers failed to provide any evidence of an exposure-risk gradient, calling into question the issue of causality of the overall association.

Medicinal Agents: The Branch conducts a variety of studies to assess drug-induced cancer. 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 the exposure usually involves high doses 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.

Cohort, case-cohort, and case-control investigations have been performed within the context of a cohort of 23,000 users of menopausal estrogens in Uppsala, Sweden. Excess risks of endometrial cancer, with evidence of dose-response relationships with both duration of use and strength of medication, were noted for estrogens unopposed by progestational agents. For those who used only the combination regimen (estrogen plus progestogen), no excess risks were noted. However, those who switched from unopposed to opposed regimens continued to show some excess risk. Evaluations of breast cancer risk revealed a 60% increase in breast cancer after 10 or more years of replacement estrogen therapy. This excess was not diminished by the addition of progesterone to the

regimen; in fact the risks were somewhat higher and seen with shorter durations of use of the combination regimen.

Oral contraceptive use is the subject of several ongoing investigations. In a study conducted in China of complete hydatidiform mole, a statistically significant trend of increasing risk with increasing years of oral contraceptive use was noted.

The Branch has continued its active program to evaluate the potential carcinogenicity of various cytotoxic agents used in the treatment of cancer and some non-neoplastic conditions. A study of second primary thyroid cancers among those treated for a first primary childhood cancer revealed a strong dose-response relationship with radiation, but no association with alkylating drug use. A similar evaluation of second primary soft tissue sarcomas uncovered excess risks for both radiation and use of alkylating drugs.

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 beta-carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, pancreas, stomach, and larynx.

A follow-up study of over 5,000 women examined in the First National Health and Nutrition Examination Survey (NHANES-I) revealed no relationship between estimates of dietary fat and saturated fat intake at baseline examination and risk of the development of breast cancer over the next ten years. Evaluation of men and women participating in NHANES-I revealed an inverse relationship between overall cancer risk and serum cholesterol measured at baseline. Those in the lowest 20% of serum cholesterol had 1.6 times the risk of malignancy of those in the highest 20%. This excess was apparent for those whose cholesterol was measured more than six years prior to the development of the disease, as well as for those measured just prior to disease. Evaluation of risk by specific anatomical site suggested a pattern of increased risks associated with lower cholesterol for a complex of smoking-related sites.

As noted previously, a variety of field investigations in high-risk areas revealed evidence of diminished risks for a number of malignancies associated with higher levels of intake of fruits and vegetables and various nutrient indices, including carotene and vitamin C. These relationships have been noted in investigations of lung cancer, stomach cancer, laryngeal cancer, pancreatic cancer, and mesothelioma. Most recently, a case-control investigation of in situ cancers of the uterine cervix indicated an elevated risk associated with relatively low dietary intake of vitamin C and particularly with low serum values of beta-carotene. Women with serum beta-carotene values in the lowest quartile had five times the risk of this malignancy as women with values in the top quartile. Similar dietary associations were not seen in a large study of invasive cancers and the serum from this study are currently being analyzed for carotene content.

A case-control, interview study of ovarian cancer in China indicated an excess risk associated with intake of animal but not plant sources of fat, with those in the highest quartile of animal fat consumption having 1.8 times the risk of those in the lowest quartile.

A series of investigations of fecal mutagenesis and colon cancer risk revealed a striking and unexpected decrease in fecapentaene excretion in cases versus controls, a decrease that could not be explained by the effects of diagnostic workup or bleeding; however, non-fecapentaene TA 98 mutagens were associated with a 4.4-fold excess risk of colon cancer. The possible dietary origins of this mutagenicity are being explored.

Investigation of the suggested relationship between alcohol intake and lung cancer risk in a large field study in New Jersey found essentially no support for this suggestion.

Case-Control Studies: The Branch conducts 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 may be 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.

Studies of breast cancer have focused on several factors in addition to those outlined under medicinal agents and nutrition. In an investigation of 266 cases of breast cancer for whom mammograms done at least four years prior to disease onset were available, a variety of radiologic parenchymal patterns were related to the risk of subsequent breast cancer. Excess risks of two- to threefold were noted for certain parenchymal patterns and these risks varied by age, family history of breast cancer, and use of menopausal hormones, but were not explained by control for recognized breast cancer risk factors. It is noteworthy that a family history of breast cancer was not a risk factor among women whose parenchymal patterns were considered N_1, the most "normal" of the parenchymal pattern classifications.

A case-control study of 358 patients with ovarian cancer revealed that parity, but not age at first birth, was inversely related to risk. In addition, hysterectomy with preservation of both ovaries was related to a decrease of ovarian cancer risk, while a variety of non-hormonal factors, including smoking and a history of childhood diseases, were not found to be related to risk.

Analyses were also conducted on the National Bladder Cancer Study data to discern the reason for the substantially reduced risk of bladder cancer among blacks compared to whites. The differences could not be explained by differences in risk factor profiles, differences in levels of risk for each factor, or by prevalence of exposure to the identified risk factors. Rather, there was some evidence, particularly from stage-specific data, to indicate that the deficit may relate to differences in completeness of ascertainment, including differential use of diagnostic services.

Infectious Agents: The discovery of several human retroviruses, notably human T-cell lymphotropic virus, type I (HTLV-I) and human immunodeficiency virus (HIV), and rapid strides in the identification of type-specific papillomaviruses in various tumors, have provided impetus to studies of an infectious etiology for some human cancers.

A case-control study of adult T-cell leukemia (ATL) in Jamaica has identified a 35-fold excess risk of ATL for persons seropositive for HTLV-I. A corollary observation is that at least 20% of the cases were negative for this antibody.

Several investigations have focused on the epidemiology of HTLV-I, especially in the West Indies. In the study of sera from 13,500 healthy Jamaican food service employees, the prevalence of antibodies to HTLV-I was 6.7%. There was a marked rise in prevalence with age, and an excess among females which emerged in the third decade of life. There were no apparent differences in prevalence of antibody according to geographic region of the island. A study in Barbados revealed a relationship between antibodies to HTLV-I and Venereal Disease Research Laboratories test positivity in the general population. A study of homosexuals in Trinidad indicated an excess prevalence of both HTLV-I and HIV. Taken together, these findings indicate that HTLV-I may also be transmitted sexually, albeit less efficiently than HIV. Studies of parenteral drug abusers in New York City, New Jersey, and New Orleans, initiated to study HIV infection, have revealed surprisingly high levels of antibodies to HTLV-I/II. The prevalence is higher in blacks (46%) than whites (11%) and is currently being pursued with more analytic investigations. A serologic survey of the prevalence of HTLV-I in lymphoreticular malignancies from various geographic locales has documented virus-positive cases from Nigeria, Israel, Taiwan, Colombia, United Arab Emirates, Panama, Singapore, Okinawa, and a number of centers in Japan.

Several other investigations in Jamaica have focused on other possible routes of transmission of HTLV-I. A minimum estimate of 45% of transfusion recipients who received HTLV-I positive blood units seroconverted after a median of 50 days. Whole blood and cellular components of blood, but not cell-free materials, were linked to seroconversions. In addition, seven of 600 children included in a measles vaccination trial tested positive for HTLV-I antibodies and upon follow-up all seven of their mothers also tested positive. Twenty percent of all of the offspring of 74 pregnant women detected as antibody positive were antibody positive also. These two observations point to the importance of ascertaining the route of likely perinatal transmission of this virus.

The program of studies of HIV, AIDS, and related issues is also ongoing. In the past year particular emphasis was placed on analysis of hemophiliac populations. Early immunodeficiency is more frequent in older (35-70 years) than younger hemophiliacs and AIDS occurs at a lower rate among the young, even among those with advanced immunodeficiency. Among the HIV infected group, the presence of p24 antigen and low T4 cell counts are strongly predictive of AIDS development. Finally the sexual partners of HIV-positive hemophiliacs who are p24 antigenemic have a three- to sixfold higher risk of HIV infection than for those whose partners do not have p24 antigen.

Suggestions that neoplasia of the uterine cervix may be largely due to type-specific papillomavirus infection are being pursued in a variety of studies.

In a study of over 700 cases and 1500 controls from Panama the relationship between papillomavirus types 16 and 18 and the risk of this disease was investigated utilizing in situ hybridization techniques on pap smear material. The relative risk associated with this infection was approximately fivefold, with the risk increasing with increased strength of the positive laboratory assay.

In a study of cervical dysplasia, papillomavirus infection and cigarette smoking were demonstrated to be independent risk factors.

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 2,900 families. Both classical and innovative analytic techniques are being applied to studies of familial aggregations of melanoma, sarcomas, genitourinary tract cancer, multiple endocrine neoplasia type 1 (MEN-1) and the nevoid basal cell carcinoma syndrome.

Molecular genetic techniques and multipoint linkage analyses have been used to map the gene for the hereditary cutaneous malignant melanoma/dysplastic nevus syndrome to the distal portion of chromosome 1p. Results were consistent in all six families studied and the multipoint lod score for the melanoma gene being located between two flanking markers was 5.42 (i.e., odds of 260,000:1 in favor of linkage). Similar techniques performed on 115 members of a single well-characterized kindred with MEN-1, confirmed the location of the gene for this syndrome on chromosome 11q13.

Assessments of genetic susceptibility to cancer outside of familial syndromes are also underway. The most noteworthy finding in this area is the pharmacogenetic study of the relationship between the metabolism of the drug debrisoquine and the risks of lung cancer. Preliminary estimates from a case-control study indicate that extensive metabolizers of this drug are at a ninefold excess risk of lung cancer, confirming the impression from a British investigation published in 1984.

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. These 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 also 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, laboratory assessments of immune status, markers of exposure to specific chemicals (particularly pesticides), and antibody responses to specific infectious agents.

Investigations this year have included evaluations in the area of papillomaviruses, fecal mutagens, and T-cell subsets. In an investigation of the reliability of southern blot analyses for papillomaviruses between independent laboratories, 40 identical samples of DNA were evaluated blindly by Southern blot tests in four laboratories with major reputations in this field. The pair-wise comparisons for presence or absence of papillomaviruses ranged between 66% and 97%, while the specification of type among those considered positive agreed between 77% and 96% of the time. Thus, much of the variability between populations which has been reported could conceivably be due to inter-laboratory variability in the assay. Studies of fecapentaene excretion indicated that various elements of the diagnostic workup for a bowel complaint did not systematically change the fecapentaene value. In addition, Ames assays of mid-polarity extracts via TA100 salmonella strains reflected almost exclusively the presence of high levels of fecapentaene. Finally, demographic variables including age, race, and sex appear to affect the "normal" values for various T-cell subsets.

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. Over 25 such reviews have been published in the past year, covering virtually all of the program areas of research covered by the Branch. Reviews of individual cancer sites have included malignant melanoma, cancer of the uterine cervix, gestational trophoblastic disease, and familial Hodgkin's disease. Reviews of issues in occupational cancer have included the relationship between chromium compounds and respiratory cancer, cancer and pesticide exposures in farmers, and herbicide exposures. Reviews of virus-related malignancies have included AIDS, retroviruses in general, and Epstein-Barr virus-related cancers. Specialized topics for review have included the relationship between carotene intake and cancer risks, diet and fecal mutagenicity, chemicals in drinking water and treatment-associated second primary cancers.

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, France 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 postdoctoral 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, 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., the acrylonitrile and methylene chloride studies); 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 (14--contracts $10,639,404) were initiated to clarify the role of various environmental and host determinants in 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 nearing completion in the San Francisco-Oakland SMSA (Standard Metropolitan Statistical Area), the Los Angeles SMSA, and Oahu, Hawaii--the only areas of the United States at the time the study was initiated 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 are 55 years of age or less, so that both they and their mothers can be interviewed about the subjects' early diet. In addition to interviewing the subjects, blood samples are being collected for hormone, lipid, and micronutrient assays; urine samples are being collected for additional hormone assays.

Cases are all women, 55 years of age or younger, 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. Approximately 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 questionnaire. 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 main objective of this series of contracts is the establishment of a collaborative research program which provides the E&B Program with resources that can be used to promptly evaluate hypotheses about environmental causes of cancer. This is accomplished by analysis of information in a prepaid health plan utilizing data recorded over many years on large groups of patients having particular cancers or exposures and comparable individuals without the cancer or exposure. Another objective has been to explore the numerous resources for record linkage within these plans in order to exploit unique opportunities for epidemiologic assessment of cancer risks. Because of the nature of prepaid health plan records, the primary hypotheses that can be tested involve those associated with the use of therapeutic drugs, medical conditions, surgical and radiologic procedures, occupations, locations of residence, and exposures that are highly correlated with any of these variables.

A number of case-control, record-abstraction studies have been supported whose primary objectives have been evaluation of a variety of medicinal agents and cancer risk. Several of these have focused on hormonal drugs, including an assessment of the risk of endometrial cancer among users of combination estrogen-progestogen regimens, and the relationship between progestogen use and ovarian cancer risk. The risk of breast cancer has been assessed in relation to use of the minor tranquilizer diazepam; and a complex evaluation of the interrelationships between histologic subtypes of benign breast disease, hormonal drug use, and a family history of breast cancer is being performed on a group of 2,615 women with benign breast disease, among whom 124 have subsequently developed breast cancer. Also currently underway is a case-control study of childhood brain tumors and in utero and childhood drug exposures, as well as parental occupation; an assessment of the prevalence of human papillomaviruses in stored pap smear slides and biopsies from women who subsequently developed cervical intraepithelial neoplasia, and the assembling of a cohort of DES-exposed mothers, sons and daughters to initiate a follow-up study. Finally, these plans have been used to assess the descriptive epidemiology of the increases over time of the incidence of breast cancer and malignant melanoma and squamous-cell cancers of the skin.

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

In the United States, pancreatic, esophageal, prostatic cancers 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 cancers, 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 micronutrient levels 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 are being selected from the population of each of these three areas. All subjects are being administered a standardized questionnaire by a trained interviewer to detect information on potential risk factors for the four cancer types. In addition, blood is being 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 papillomaviruses, although these agents have 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, for which data collection has been completed, 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 were approximately 750 women with invasive cervical cancer from four Latin American countries (Colombia, Costa Rica, Mexico, and

Panama) and 1,500 matched controls. Personal interviews were conducted with these women, and blood and cervical scraping material obtained. In addition, the study included male subjects, who comprised the husbands of the sexually monogamous women. These male study subjects were interviewed in conjunction with a physical examination that focused on hygiene, circumcision status and evidence of infection. Blood samples and penile scrapings were also 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., infectious agents and micronutrients) to risk of these cancers.

The study, which has recently been completed, utilized 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 were chosen for each case in both study sites.

An attempt was made to conduct personal home interviews with each case and control subject. Topics of the interview included: demographic characteristics, socioeconomic status, reproductive history, sexual history, menstrual history, general medical history including history of premalignant vulvar lesions, smoking history, use of contraceptives, and dietary history. Pertinent data was also abstracted from the medical records of cases. In addition, 30 ml of venous blood was 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 were 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.

Data collection is completed, and analysis has started for a population-based study in the state of Iowa that used mail questionnaires to collect information from cases (or surrogates) and controls. The study was designed 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 entailed 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 is being used to estimate past exposures of respondents. Included in the study are approximately 3,000 cases and 1,600 controls.

Expansion of an Ongoing Case-Control Study of Cancer and Drinking Water Contaminants (1 Contract):

A two year continuation of the "Case-Control Study of Cancer and Drinking Water Contaminants" will include 800 additional cases of bladder cancer and appropriate controls to add to the 600 bladder cases in the original study. This will permit us to further evaluate risk associated with consumption of chlorinated surface water, and explore the question of interaction with other risk factors, such as cigarette smoking.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 89

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 Charles Lynch NO1 CP 51026	Case-Control Study of Cancer and Drinking Water Contaminants
University of Iowa Charles Lynch NO1 CP 85614	Expansion of an Ongoing Case-Control Study of Cancer and Drinking Water Contaminants

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04378-14 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
U.S. Cancer Mortality Survey and Related Analytic Studies

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

PI:	R.N. Hoover	Chief	EEB	NCI
Others:	N.A. Dalager	Epidemiologist	EEB	NCI
	R.T. Falk	Health Statistician	EEB	NCI
	B.L. Stephenson	Computer Specialist	BB, DCE	NCI
	R.I. Ramsbottom	Computer Specialist	BB, DCE	NCI
	J.M. Stump	Chief, Info. Resources Sec.	BB, DCE	NCI

COOPERATING UNITS *(if any)*
National Center for Health Statistics, Bureau of the Census (Sam Davis); 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
1.25	1.1	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 twofold: 1) through descriptive studies to explore the geographic, racial, ethnic, time-trend and other patterns of cancer mortality in the U.S., and 2) through analytic field investigations in areas of special risk to generate and/or test hypotheses to explain the descriptive variation noted.

PROJECT DESCRIPTION

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

R.N. Hoover	Chief	EEB	NCI
R.T. Falk	Health Statistician	EEB	NCI
B.L. Stephenson	Computer Specialist	BB, DCE	NCI
R.I. Ramsbottom	Computer Specialist	BB, DCE	NCI
J.M. Stump	Chief, Info. Resources Sec.	BB, DCE	NCI

Objectives:

The overall objective of this project is twofold: 1) through descriptive studies to explore the geographic, racial, ethnic, time-trend and other patterns of cancer mortality in the U.S., and 2) through analytic field investigations in areas of special risk to generate and/or test hypotheses to explain the descriptive variation noted.

Methods Employed:

Methods for the descriptive component of this project involve computer analysis of more than nine 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. For the analytic phase of this project the usual approach is that of a case-control study of site-specific cancers among residents of the selected geographic areas, utilizing appropriate comparison persons.

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 among nonwhites relative to the country as a whole. Ongoing analyses of this data resource suggest that nonwhite prostate cancer mortality is increasing rapidly in the southeastern U.S.

Long-standing excesses of lung and other tobacco-related malignancies have been noted for some time in southern Louisiana. In addition, while the cancer maps showed little evidence of clustering of high rates for pancreatic cancer, southern Louisiana was one of the few areas of such clustering. Finally, while stomach cancer rates were elevated among Blacks, little evidence of clustering was seen in the maps for nonwhites, with the notable exception of a broad area of elevated rates in southern Louisiana. For all these reasons, a series of hospital-based, case-control studies of lung (n=1338), pancreas (n=363), and stomach (n=391) cancers were conducted in this area in collaboration with Louisiana State University.

Analysis of the pancreatic cancer study yielded no evidence of occupational risks in the oil and gas extraction or petroleum refining industries. Some excesses were noted for truck driving and for electronic assembly and

repair. Analysis of a large number of dietary variables yielded evidence of excess risks associated with pork and rice consumption and a strong protective influence for fruit intake.

The gulf coast areas of Texas were noteworthy for marked excesses of respiratory cancers (primarily lung and larynx). These observations, along with correlational studies suggesting a hazard associated with the presence of the petrochemical industry, led to investigations of these two sites in collaboration with the University of Texas. Detailed evaluation of the implication of a family history of malignancy in the lung cancer study indicated a 1.5-fold increased risk associated with a family history of cancer in a first-degree relative which rose to a threefold excess when two or more first-degree relatives had been diagnosed with lung cancer.

Analyses of tobacco and alcohol use in laryngeal cancer cases and controls identified a dose-dependent relationship between level of risk and usual number of cigarettes smoked, the relative risk rising from fourfold for one-half pack/day to tenfold for two packs/day. A dose-related relationship between risk and alcohol consumption was noted, but only for supraglottic laryngeal cancer cases.

Perhaps the most prominent state highlighted by the cancer maps in the mid-1970s was New Jersey, which was promptly labeled "cancer alley" by the lay press. Over the years the EEB has pursued a number of these excesses in collaboration with the New Jersey State Department of Health. Most recently, a series of population-based studies of lung cancer (763 white males, 296 black males, and 994 females) have come to analysis. While most of the analyses still have to be done, a few findings have emerged. Analysis of lifetime occupational histories noted excess risks for masons, tilesetters, janitors, printing workers, trucking service, warehousing, and storage workers. Analyses have also been done exploring the relationship between tar content of cigarettes smoked and risk of lung cancer and clarifying the protective role of fruit, vegetables and carotene consumption.

Publications:

Correa P, Fontham E, Chen V, Craig J, Falk R, Pickle LW. Diet, nutrition and cancer. J La Med Soc 1988;140:43-9.

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Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr. Lifestyle risk factors for pancreatic cancer in Louisiana. A case-control study. Am J Epidemiol 1988;128(suppl 2):324-36.

Fontham ETH, Correa P, Chen VW, Craig J, Pickle LW, Falk R. Tobacco and cancer. J La Med Soc 1988;140:29-39.

Fontham ETH, Pickle LW, Haenszel W, Correa P, Lin Y, Falk RT. Dietary vitamin A and C and lung cancer risk in Louisiana. Cancer 1988;62(suppl 10):2267-73.

Hayes HM, Jr, Pickle LW, Burt JK, Wilson GP. Feline hip dysplasia. Radiographic study of 300 asymptomatic patients. Cornell Vet (In Press).

Mackerras D, Buffler PA, Randall DE, Nichaman MZ, Pickle LW, Mason TJ. Carotene intake and the risk of laryngeal cancer in coastal Texas. Am J Epidemiol 1988;128:980-8.

Mason TJ, Prorok PC, Saccomanno G, Archer BE. Effects of cigarettes and radiation on cytologic changes in sputum. Cancer Res (In Press).

Paul LD, Brantly ML, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with ãl-antitrypsin deficiency of adults with pulmonary symptoms. Am Rev Respir Dis 1988;138:327-36.

Pickle LW, Mason TJ, Fraumeni JF Jr. The new U.S. cancer atlas. Recent Results in Cancer Research 1989;114:196-207.

Pickle LW, Mason TJ, Howard N, Hoover R, Fraumeni JF, Jr. Atlas of U.S. Cancer Mortality Among Nonwhites, 1950-1980. Washington, DC: U.S. Government Printing Office (In Press).

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Schiffman MH, Pickle LW, Fontham E, Zahm SH, Falk R, Mele J, Correa P, Fraumeni, JF Jr. A case-control study of diet and mesothelioma. Cancer Res 1988;49:1322-6.

Wilcox HB, Schoenberg JB, Mason TJ, Bill JS, Stemhagen A. Smoking and lung cancer: risk as a function of cigarette tar content. Prev Med 1988;17:263-72.

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

Person 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: $1,535,900

Person 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: Z01CP04410-13 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

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	Chief, Family Studies Section	EEB	NCI
Others:	S.J. Bale	Senior Staff Fellow	EEB	NCI
	N.E. Caporaso	Biotechnology Fellow	EEB	NCI
	G.L. Shaw	Medical Staff Fellow	EEB	NCI
	A.M. Goldstein	IRTA Fellow	EEB	NCI
	C.I. Amos	IRTA Fellow	EEB	NCI
	M.C. Fraser	Clinical Nurse Specialist	EEB	NCI
	D.L. Mann	Chief, Immunogenetics Sec.	LVC	NCI

COOPERATING UNITS *(if any)*
Biological Research Faculty & Facility (T. Williams); Braton Biotech (S. VedBrat); Biotech Laboratories (D. Ringer); Westat, Inc. (J. Cahill); ARC (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, bulk culture, and DNA extraction 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 located on 1p36) and biological (enhanced sensitivity to the cytotoxic and mutagenic effects of UV radiation) risk factors have been identified. The therapeutic administration of cytotoxic drugs provides an opportunity to explore the carcinogenic effects of these agents in man. Case-control and cohort studies of cancer patients treated with specific cytotoxic drugs are conducted. These studies have documented differences in leukemogenic potential among specific alkylating agents, and increasing risk of bone cancer associated with alkylating agents independent of radiation therapy has been demonstrated.

PROJECT DESCRIPTION

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

M.A. Tucker	Chief, Family Studies Section	EEB	NCI
C.I. Amos	IRTA Fellow	EEB	NCI
S.J. Bale	Senior Staff Fellow	EEB	NCI
N.E. Caporaso	Biotechnology Fellow	EEB	NCI
M.C. Fraser	Nurse Epidemiologist	EEB	NCI
A.M. Goldstein	IRTA Fellow	EEB	NCI
G.L. Shaw	Medical Staff Fellow	EEB	NCI
D.L. Mann	Chief, Immunogenetics Section	LVC	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, 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. 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 or contract laboratories. For studies of cytotoxic drugs, standard cohort and case-control methods are used.

Major Findings:

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 2900) 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. This system includes a computerized clinical information file which can be linked to a biospecimen inventory and laboratory-generated data files, thus simplifying record keeping and permitting computer-based data analysis. An additional component is a computerized patient, test and record tracking system designed to permit efficient monitoring of the information generated. Three contracts, shared with the Viral Epidemiology Section, 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 (Biological Research Faculty and Facility); 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 genetic linkage studies (American Type Culture Corporation, Integrated Genetics, Inc. and University of California at Los Angeles). 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 critical quantitative approaches to the design and analysis of studies conducted in members of cancer-prone families.

Malignant Melanoma

This project is now in its thirteenth year, employing the interdisciplinary research strategy outlined above. The gene for familial melanoma has been mapped to 1p36. Additional families have been examined and DNA collected to confirm the finding. The study to evaluate fragile sites in affected members of melanoma-prone families has continued. The data have been collected and the analysis is in progress.

The pilot study of dysplastic nevi in a dermatology practice is in analysis. The data will be useful in the design of the multi-center cutaneous melanoma case-control study. Preliminary analysis has revealed that 80% of the dysplastic nevus cases have family members with dysplastic nevi.

Genitourinary Cancer

Members of previously studied bladder cancer families in the younger generation are now approaching the age when they might start to develop bladder cancer. Members of these families prone to bladder cancer are being recontacted to undergo an extensive clinical and pharmacogenetic evaluation.

Nevoid Basal Cell Carcinoma Syndrome:

Studies to find the genomic location of the NBCC gene are ongoing. Linkage studies using 26 polymorphic biochemical markers are complete and investigations using DNA markers are still in progress. Chromosome fragility studies in the syndrome demonstrate no excess of sister chromatid exchange or chromatid breaks.

In collaboration with the Dermatology Branch, NCI, we are beginning to analyze the relationship between lifetime sun exposure and development of basal cell carcinomas in affected individuals. An educational "UPDATE" has been developed and is sent annually to all family members who have participated in the study as well as to referring physicians and other interested dermatologists and geneticists.

Multiple Endocrine Neoplasia Type I (Wermer's Syndrome):

One hundred fifteen members of a single, well-characterized kindred, including 44 affected individuals have been evaluated. Analysis of linkage with 26 polymorphic biochemical markers has been completed and presented at an international meeting. Linkage studies using DNA markers confirmed the finding of a gene for MEN1 located on human chromosome 11q13. A multipoint linkage analysis of the marker data created a map of that region of 11q.

DNAs have been prepared from individuals in six other families with MEN1, or variants of the syndrome, and linkage analyses are underway.

Breast Cancer

Genetic analysis of the family history data from the Cancer and Steroid Hormone Study is underway.

Biochemical Epidemiology of Lung Cancer:

As one of the initial EEB efforts in applying sophisticated laboratory probes to an epidemiologically-designed study, a case-control study of lung cancer has been completed and is being analyzed.

Preliminary analysis confirms that the debrisoquine extensive metabolizer phenotype is related to the risk of lung cancer. There are also differences in the distributions of phenotypes in blacks and whites. Laboratory components of this study include evaluating 1) a RFLP marker thought to be close to the gene for the enzyme for debrisoquine metabolism; 2) polymorphisms at the c-H-*ras* locus variable tandem repeat region; 3) urine mutagenesis; 4) urinary n-nitrosoacids; and 4) 4-aminobiphenyl hemoglobin adducts.

Reanalysis of Idle's data set continues. Redefinition of metabolic phenotypes improved the estimation of gene frequencies. The analysis of the occupational data has shown an additive effect of the extensive debrisoquine metabolic phenotype and asbestos or polyaromatic hydrocarbons. A large multicenter case-control study of lung cancer in collaboration with the Lung Cancer Study Group

has been initiated to confirm the above observations. This study is in the pilot phase of field work at the Naval Medical Command National Capital Region (NMCNCR).

PROJECT 2: THE CARCINOGENICITY OF CYTOTOXIC DRUGS

Employing various strategies, this project is designed in collaboration with the Radiation Epidemiology Branch (REB), NCI, 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.

Among the strategies employed are: (1) cohort studies of patients with a particular index disease; (2) randomized cohort studies, similar to (1) except that patients are participants in randomized clinical trials; and (3) case-control studies of patients with second cancers.

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. 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. Preliminary analyses of connective tissue sarcomas also shows an effect of alkylating agent chemotherapy in addition to radiation therapy.

Ovarian Cancer:

A collaboration with the Gynecologic Oncology Group to evaluate the carcinogenicity of cis-platin and adriamycin, as well as to update the previously studied cohorts has been initiated.

Publications:

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Caporaso N, Hayes R, Dosemeci M, Hoover R, Ayesh R, Hetzel M, Idle J. Lung cancer risk, occupational exposure, and the debrisoquine metabolic phenotype. Cancer Res (In Press).

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Dracopoli NC, Bale SJ. Genetic aspects of familial cutaneous malignant melanoma. Semin Oncol 1988;15:541-8.

Dracopoli NC, Harnett P, Bale SJ, Stanger BZ, Tucker MA, Housman DE, Kefford RF. Loss of alleles from distal chromosome 1p occurs late in melanoma tumor progression. Proc Natl Acad Sci USA (In Press).

Fraser MC. Measuring mental status and level of consciousness. In: Instruments for clinical nursing research. Norwalk: Appleton and Lange, 1988; 47-78.

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Osterlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: I. Importance of host factors. Int J Cancer 1988;42:200-6.

Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: II. Importance of UV-light exposure. Int J Cancer 1988;42:319-25.

Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: III. Hormonal and reproductive factors in women. Int J Cancer 1988;42:821-4.

Osterlind A, Tucker, MA, Stone, BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: IV. No association with nutritional factors, alcohol, smoking or hair dyes. Int J Cancer 1988;42:825-8.

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Tucker MA. Cancer, Hodgkin's disease, familial. Birth Defects Encyclopedia (In Press).

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Tucker MA, Bale SJ. Clinical aspects of familial cutaneous malignant melanoma. Semin Oncol 1988;15:524-8.

Tucker MA, Boice JD, Hoover RN. Second cancers following retinoblastoma. [Letter to Editor]. N Engl J Med 1988;318:581.

Tucker MA, Coleman CN, Rosenberg SA. Young women treated with mantle radiotherapy for Hodgkin's disease. (Reply to Letters to the Editor). N Engl J Med 1988;319:244.

CONTRACTS IN SUPPORT OF THIS PROJECT

BIOLOGICAL RESEARCH FACULTY AND FACILITY, INC. (NOI-CP7-1025-00)

Title: Biological Specimen Repository for Patients at High Risk for Cancer

Current Annual Level: $203,522

Person Years: 2.05

Objectives: To maintain repository of fibroblasts and tumor cell lines, to grow to bulk culture selected cell lines, and to initiate new cell lines from individuals at increased risk of cancer.

Major Contributions:

The laboratory was sent 7 established cell lines and 27 skin biopsy specimens to establish fibroblast lines. A total of 285 samples were dispersed to 10 destinations. Eighteen cell lines were grown to 1/4 gm quantities. A total of 174 new vials of human fibroblast were stored in liquid nitrogen freezers. Ten blood samples were transformed with EBV. The cells grown to bulk are used to extract DNA for gene mapping studies.

AMERICAN TYPE CULTURE COLLECTION (Subcontract to Microbiological Assoc., Inc.; NO1-CP5-1029)

Title: Transformation of normal human lymphocytes, preparation of bulk culture of normal human lymphoblastoid cell lines and DNA extraction (MBA-1029-25; MBA-1029-27; MBA-2039-29)

Current Annual Level: $300,000

Person Years: 6.6

Objectives: To establish lymphoblastoid cell lines from human lymphocytes, to prepare bulk cultures of lymphoblastoid cells and to extract DNA from whole blood, human cell lines and tumor. The DNA is then used in genetic studies and gene mapping.

Major Contributions: One hundred frozen lymphocyte samples are currently being transformed, and cell lines established. DNA has been prepared from approximately 25 samples of fresh whole blood.

INTEGRATED GENETICS, INC. (NO1-CP7-1127)

Title: Genetic factors in persons at high risk of cancer (Assay B-DNA Polymorphisms)

Current Annual Level: $378,122

Person Years: 4.1

Objectives: To provide DNA polymorphism typings on samples submitted for use in genetic linkage studies.

Major Contributions: The lab has thus far performed 390 assays on 78 persons with multiple endocrine neoplasia type 1 (MEN1) and another 468 assays are in progress. The information from this study has contributed to the mapping of the gene for MEN1. In an effort to locate the gene for Li-Fraumeni syndrome, a further 480 assays of paired tumor/constitutive DNAs are in progress.

REGENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES (NO1-CP7-1081)

Title: Genetic factors in persons at high risk of cancer (Assay A-Protein Polymorphisms)

Current Annual Level: $56,355

Person Years: .35

Objectives: To provide red blood cell, serum and plasma typings for a panel of 30 polymorphic genetic markers for use in genetic linkage studies.

Major Contributions: The laboratory has received samples from 255 individuals in 14 families for analyses of eight hereditary disorders. The results of these studies have contributed to the mapping of the genes for multiple endocrine neoplasia type 1, hypertrophic cardiomyopathy and hereditary cutaneous malignant melanoma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04411-13 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

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:	K.P. Cantor	Epidemiologist	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	L.W. Pickle	Statistician	EEB	NCI
	R.E. Tarone	Statistician	BB, DCE	NCI
	B. Sass	Veterinary Medical Officer	OD, DCE	NCI

COOPERATING UNITS *(if any)*
Purdue University (R. Richardson), Colorado State University (D. McCurnin)
Ohio State University (W. Beard), University of Minnesota (C. Jessen)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Environmental Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.2	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 veterinary studies area conducts epidemiologic studies to evaluate the role environmental factors have on the etiology of cancer in companion to domestic animals, and to identify situations where the companion animal may serve as a sentinel for man for environmental carcinogens. Major areas of current interest include yard and garden herbicides and pesticides; in-home use of pesticides, cleaning-solvents; in-home exposure to inorganic dusts and radon. A case-control study is underway using owner supplied data evaluating chemical exposures among dogs with malignant lymphoma and matched tumor and non-tumor controls. Preliminary findings point to a significant association between the use of professional lawn chemical services and/or owner application of weed killers and canine malignant lymphoma. A case-control study of canine bladder cancer shows positive associations with community water supply, professional grooming salons, and owner applied flea and tick dip. Other topics of interest include the epidemiology of canine gastric carcinoma and prostatic carcinoma.

PROJECT DESCRIPTION

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

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

Objectives:

To conduct epidemiologic studies to 1) identify situations where companion domestic animals which may serve as early predictors of environmental hazards to humans, 2) clarify the role specific home-related factors play in the etiology of cancer, and 3) generate hypotheses for promising areas of research.

Methods Employed:

Analytical studies of animals with suspected environmental-related cancer are identified from medical record abstracts supplied on contract to the Branch by U.S. and Canadian veterinary university teaching hospitals; selected control animals are selected from the same source. Owner names and addresses are obtained from collaborating institutions and information is sought concerning the home environment, use of yard and garden chemicals, household chemicals, food and drinking water, exposure opportunities, and household history of cancer using a mailed questionnaire. A telephone interview is used in instances of non-response. Descriptive studies utilize veterinary hospital data (2.8 million hospital episodes) to assess risk factors associated with age, breed, sex, neuter status, associated medical conditions, geographic location, and temporal effects.

Major Findings:

1. Preliminary results of a case-control study (591 cases, 1,182 controls) of canine malignant lymphoma, a condition considered similar to non-Hodgkin's lymphoma in humans, shows a significant association (OR=1.3) with owner employment of professional lawn chemical services and/or owner application of 2,4-D to lawns accessible to the pet. Other positive associations were with cases living in homes with basements and owner use of carpet cleaners/deodorizers.

2. Preliminary results of a case-control study of (101 cases, 404 controls) canine bladder cancer show positive associations with community water source, being professionally groomed, owner applied flea and tick dip, exposure to house paints and solvents and dry-cleaned drapes.

3. A study of 279 dogs with an aortic body tumor (ABT), 67 with a carotid body tumor (CBT), and 11 with both tumors showed distant metastases, mostly to the

lungs and liver, in 12% of the ABT cases and 16% of those with CBT. As in man, dogs experienced certain other concomitant neoplasms. These second primary tumors were more evident in dogs with ABT than CBT. The most frequent were thyroid carcinomas, interstitial cell tumors, and seminomas.

4. A retrospective study of 250,000 horses seen in clinic identified squamous cell carcinoma (SCC) of the aglandular stomach as the most common gastrointestinal carcinoma (N=64). With the exception of man, spontaneous alimentary carcinomas are rare in monogastrics. Most originate from glandular epithelium except in the rat and mouse, and the horse. The etiology of equine gastric SCC is unclear, but based on experimental work with laboratory rats and mice, species whose gastric anatomy resembles that of the horse, several etiologic hypotheses seem plausible.

Considerable bacterial fermentation of ingested food takes place in the aglandular equine stomach allowing it to be exposed to the reduction of ingested nitrates to nitrites and/or to the nitrosation of protein substrates (amines and amides) to form carcinogenic nitrosamines and nitrosamides. The source of the dietary nitrates may be feedstuffs themselves and/or nitrate contaminated water. In the laboratory rodent, N-nitroso compounds given orally or by stomach tube typically induce gastric SCC, with and without accompanying glandular gastric carcinoma.

Another etiologic mechanism may involve a reaction to feedstuffs or water contaminated with carcinogenic polycyclic aromatic hydrocarbons [e.g. benzo(a)pyrene]. Carcinogenic polycyclics, when fed orally to mice or placed directly on the gastric mucosa of rats have been shown to induce aglandular SCC rather than carcinoma of the glandular stomach. This induction was greatly enhanced in rodents when the carcinogen was administered in the presence of mineral oil, a common substance routinely used as an equine purgative.

5. A prospective pelvic radiographic study of 300 asymptomatic cats brought to veterinary attention for reasons other than mobility dysfunction or known skeletal abnormalities identified 30 with mild-to-severe hip dysplasia. A significant positive association was evident between body weight, incidence, and severity of the condition. There was no detectable familial risk.

Publications:

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Sass B, Rehm S, Hayes HM. Histologic classification with notes on the epidemiology of canine gastric carcinoma. J. Vet. Med. [A] (In Press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04480-13 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

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.E. Blair	Chief, Occupational Studies Section	EEB	NCI
Others:	M. Dosemeci	Visiting Fellow	EEB	NCI
	M.R. Gomez	Industrial Hygienist	EEB	NCI
	R.B. Hayes	Epidemiologist	EEB	NCI
	E.F. Heineman	IRTA Fellow	EEB	NCI
	L.M. Pottern	Epidemiologist	EEB	NCI
	P.A. Stewart	Industrial Hygienist	EEB	NCI
	S.K. Zahm	Epidemiologist	EEB	NCI

COOPERATING UNITS *(if any)*
Univ. of NE (D. Weisenberger); Univ. of NC (C. Shy); U.S. Coast Guard (T. Haas); USDA (J. Teske); Univ. of IA (B. Kross); NIOSH (H. Amandus, R. Herrick); MO Cancer Control Program (R. Brownson), Danish Cancer Registry (J. Olsen)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Occupational Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
11.5	8.5	3.0

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

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

The Occupational Studies Section conducts epidemiologic studies to determine the role occupational exposures play in the origin of cancer. Major areas of focus include pesticides, organic solvents and other widely used chemicals, and organic and inorganic dusts. Studies of agricultural-related occupations uncovered elevated risks for leukemia among extension agents, non-Hodgkin's lymphoma among soil and forest conservationists, and soft-tissue sarcoma among farmers using animal insecticides. A cohort study of Coast Guard marine inspectors exposed to a variety of chemicals while inspecting ships and barrages uncovered excess deaths from motor vehicle accidents, cirrhosis of the liver, leukemia, and liver cancer that rose with increasing levels of exposure. Physical activity occurring on the job was associated with a reduced risk of colon cancer in two studies. Studies of tobacco use suggest that smoking increases the risks of leukemia, particularly myelogenous leukemia, and that smokeless tobacco is associated with soft-tissue sarcoma. Mortality from leukemia and non-Hodgkin's lymphoma was elevated among furniture workers. Lung cancer was excessive among hematite miners exposed to silica and radon and among workers exposed to chrome pigments. Major efforts underway include investigations of industrial workers exposed to acrylonitrile, grain millers exposed to fumigants, workers in dusty trades exposed to silica, workers in China exposed to benzene, lawn care workers and agricultural applicators exposed to herbicides, and embalmers exposed to formaldehyde. Methodologic studies are being conducted to improve exposure assessment procedures and to develop a referent data base composed of workers.

PROJECT DESCRIPTION

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

A.E. Blair	Chief, Occupational Studies Section	EEB	NCI
M. Alavanja	Special Assistant	E&B	NCI
L. Brown	Epidemiologist	BB	NCI
K.P. Cantor	Epidemiologist	EEB	NCI
M. Dosemeci	Visiting Fellow	EEB	NCI
J.F. Fraumeni	Associate Director	E&B	NCI
M. Gomez	Industrial Hygienist	EEB	NCI
R.B. Hayes	Epidemiologist	EEB	NCI
E. Heineman	IRTA Fellow	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
L.M. Pottern	Epidemiologist	EEB	NCI
J. Sontag	Special Assistant	E&B	NCI
P.A. Stewart	Industrial Hygienist	EEB	NCI
S.H. Zahm	Epidemiologist	EEB	NCI

Objectives: The Occupational Studies Section conducts a comprehensive program of occupational studies to evaluate the role factors in the workplace play in the origin of cancer. The primary focus of this project is to identify and clarify the role that specific occupational factors play in human carcinogenesis by integrating industrial hygiene evaluation into study designs.

Methods Employed: To accomplish program objectives the Section conducts: a) descriptive and hypothesis-generating studies of occupations and industries to identify promising areas of research and to sharpen hypotheses, b) analytic studies with detailed industrial hygiene components to evaluate the carcinogenicity of specific occupational exposures, c) industrial hygiene investigations to evaluate workplace exposures and to improve methods of exposure evaluation in epidemiologic studies, and d) projects to improve epidemiologic methods and to develop resources for occupational studies.

Major Findings:

1. Cancer excesses have been noted in several groups exposed to pesticides. Soft-tissue sarcoma was elevated among farmers exposed to animal insecticides (1.6-fold). The results rose to nearly fivefold among those first exposed in the 1940's and appeared to be most strongly linked to organochlorine insecticides. Leukemia was elevated (approximately twofold) among agricultural extension agents from the U.S. Department of Agriculture who may have contact with pesticides, while non-Hodgkin's lymphoma was excessive (approximately 2.5 fold) among soil and forest conservationists. In nested case-control analyses, the risk of lymphatic leukemia rose to 5.4 among extension agents employed for 15 or more years, while non-Hodgkin's lymphoma rose to threefold among persons employed as conservationists for 15 or more years.

2. Using data from the Missouri Tumor Registry, the risk of colon cancer was found to decrease with increasing levels of physical activity required on the job (relative risk in a high activity job was 0.7 that of a low activity job), particularly for the descending colon and cecum. Similar results were obtained in a study using the NHANES follow-up data where the relative risks of colorectal cancer among men with high activity jobs was 0.6 compared to inactive jobs. In the NHANES data this association persisted after adjustment for various potential confounders including smoking, body mass index, socioeconomic status, and dietary fat.

3. Excessive mortality from lung cancer (SMR=3.7) occurred among underground haematite miners compared to above ground miners. Risk was greater among miners with heavy exposure to dust and radon (SMR=4.2), or with silicosis (SMR=5.3).

4. Coast Guard marine inspectors with exposure to a variety of organic solvents and other chemicals had elevated mortality from cirrhosis of the liver (RR=1.9), motor vehicle accidents (RR=1.4), liver cancer (3 deaths vs. 0 deaths) and leukemia (RR=2.0) compared to other Coast Guard officers. Risks for these diseases rose with increasing cumulative exposure to chemicals.

5. A study of over 36,000 furniture workers uncovered elevated mortality from leukemia (SMR=2.0) and non-Hodgkin's lymphoma (SMR=2.0) among white men employed in the manufacture of wooden furniture. Metal furniture workers experienced a significant excess of all cancers combined (SMR=1.6) with non-significant excesses for cancers of the lung, stomach, and colorectum.

6. An evaluation of occupational risks for histologic types of lung cancer noted associations between adenocarcinoma of the lung and employment as (furniture workers (OR=2.0), plumbers (OR=2.1), printers (OR=1.8), electricians (OR=1.5), and welders (OR=1.7). Excesses for squamous cell cancer of lung occurred among policemen and firefighters (OR=1.8), brickmasons (OR=1.7), roofers (OR=2.2) and welders (OR=1.7).

7. As part of the effort to improve exposure assessment projects new semi-qualitative methods were developed to fully exploit the availability of historical information. A procedure developed for case-control studies involved making estimates of exposure by occupation and industry separately and using an algorithm to develop estimates for occupational/industry combinations. This new procedure reduced the number of estimations performed by the industrial hygienists in the traditional approach requiring a separate evaluation for each occupation/industry combination from 13,445 workers in one study to 2,000 in another study. Yet the exposure estimates from the two procedures agreed 89% of the time.

8. An excess risk of lung cancer was found among chromium pigment workers that rose to over 3-fold among those employed 10 or more years.

9. A 1.8-fold excess of soft-tissue sarcoma occurred among subjects using smokeless tobacco, the first time these cancers have been associated with tobacco use. The risk was greater for tumors of the upper gastrointestinal tract (OR=3.3), lung and pleura (OR=3.1) and head, neck and face region (OR=2.4) than for other regions of the body (OR=1.4).

Publications:

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CONTRACTS IN SUPPORT OF THIS PROJECT

ORI, INC. (NO1-CP-61039)

Title: Support Services to Develop a Computerized Comparison Population for Occupational Studies

Current Annual Level: $45,803

Person Years: 1

Objectives: To assemble data from completed NCI and NIOSH cohort mortality studies and to develop a comparison population of workers for use in epidemiologic studies.

Major Contributions:

Completed cohorts from NIOSH and NCI have been received and have been arranged in a standardized format. Programs are being developed to construct matrices of reference rates that can be provided to investigators.

SRA TECHNOLOGIES, INC. (NO1-CP-41022)

Title: Mortality Study of Workers Exposed to Acrylonitrile.

Current Annual Level: $94,094

Person Years: 2

Objectives: To provide data collection services for a cohort mortality study of workers exposed to acrylonitrile in eight plants.

Major Contributions:

A cohort of over 25,000 workers has been assembled from personnel records for the eight participating plants. Complete work histories have been abstracted and keyed. A ten percent sample of the cohort is being interviewed to obtain information on smoking. Tracing of study subjects is underway to determine vital status. Industrial hygiene monitoring has been conducted in each of the plants.

WESTAT, INC. (NO1-CP-51018)

Title: Support Services for Occupational Studies.

Current Annual Level: $460,771

Person Years: 15

Objectives: To provide data collection and data management services for occupational studies. Activities include abstracting and interviewing, keying, coding, and editing of the data, monitoring and assessing occupational exposures, tracing study subjects, and performing statistical tabulations.

Major Contributions:

During the past fiscal year approximately 20 projects have received support under this contract. These have included projects such as case-control studies of lymphatic and hematopoietic cancer and pesticide exposure in Nebraska, of brain cancer and leukemia among embalmers, lung cancer among pesticide applicators, cohort mortality studies of lawn care workers, aerial applicators, firefighters, plumbers and pipefitters, dry cleaners, jewelry workers, chemists, shipyard workers, Coast Guard marine inspectors, noxious weed applicators and furniture workers. Support was provided for a feasibility study of workers exposed to methylene chloride and preliminary exposure evaluation in funeral homes. Methodologic studies to improve and compare procedures used to estimate historical exposures were also supported.

UNIVERSITY OF IOWA (NO1-CP-95602)

Title: Exposure Assessment Methods for Pesticides

Current Annual Level: $236,087

Person Years: 4

Objectives: To improve procedures used to assess historical exposures to pesticides.

Major Contributions:

Contract was awarded in April 1989. Work has only just begun.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05128-10 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

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:	R.G. Ziegler	Nutritional Epidemiologist	EEB	NCI
Others:	L.A. Brinton	Chief, Environmental Studies	EEB	NCI
	K.E. Brock	IRTA Fellow	EEB	NCI
	J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
	G. Gridley	Statistician (Health)	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	C.J. Jones	Staff Fellow	EEB	NCI
	M.H. Schiffman	Clinical Investigator	EEB	NCI

COOPERATING UNITS *(if any)*
NCHS (J Madans);NIST (N Craft, S Margolis);CA Tum Reg (D West);Univ of HI (A Nomura);USC (B Henderson);Kaiser Hlth Plans (A Glass);Walter Reed Army Med Ctr (J Daniel);Beth Naval Hosp (A Robinson);GWU Hosp (L Smith)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Environmental Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.1	2.6	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.)*

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 beta-carotene; and storage and cooking practices. Cancers being studied include those of the breast, colon, endometrium, ovary, cervix, oral cavity and pharynx, and prostate. 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	Nutritional Epidemiologist	EEB	NCI
L.A. Brinton	Chief, Environmental Studies	EEB	NCI
K.E. Brock	IRTA Fellow	EEB	NCI
J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
G. Gridley	Statistician (Health)	EEB	NCI
R. Herrero	Visiting Fellow	EEB	NCI
A. Hildesheim	CEBTP Fellow	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
C.J. Jones	Staff Fellow	EEB	NCI
M.H. Schiffman	Clinical Investigator	EEB	NCI
X.O. Shu	Visiting Fellow	EEB	NCI

Objectives:

(1) To assess, in human populations, specific hypotheses concerning the relationship of diet, nutrition and cancer that have been suggested by biochemical, animal, clinical, and epidemiologic studies. (2) To test systematically for associations between diet and nutrition and specific cancers and to generate hypotheses about the nature of any relationships detected. (3) To develop and validate methods for nutritional epidemiology, including dietary questionnaires, nutrient measurements, and analytic approaches. (4) To develop and utilize national nutrition data resources. (5) To elucidate the basic biology of carcinogenesis through studying the influence of diet on cancer in human populations.

Methods Employed:

1. Within the context of the case-control study among participants in the Breast Cancer Detection Demonstration Project (BCDDP), described in project Z01CP05526-03 EEB, measured height and weight during screening enabled the evaluation of body size as a risk factor for the development of breast cancer.

2. In the continuation of the follow-up activities within the BCDDP cohort, a dietary component has been added to the mailed questionnaire. This will enable a number of nutritional hypotheses to be tested. The interview also includes questions on physical activity, alcohol use throughout life, and changes in weight and relative weight.

3. When Asian women migrate to the U.S., their low rates of breast cancer rise toward American rates over several generations as they adopt a more Westernized diet. To assess the effect of diet on breast cancer risk, a population-based case-control interview study is nearing completion among Asian-American women in Los Angeles, San Francisco, and Oahu. Approximately 800 Chinese, Japanese, and Filipino cases diagnosed during 1983-87 have been interviewed. The study population is limited to subjects 55 years or younger so that mothers could also be interviewed about the subjects' early diet and life-style. The influence on breast cancer risk of age at migration to the U.S. and non-dietary

aspects of acculturation will be analyzed. Several months after diagnosis and treatment, fasting plasma and 12-hour urines were collected for hormone, lipid, and micronutrient determinations.

4. Although colorectal cancer mortality rates for white men and women are about 50% lower in the south than in the north, within the 11 Florida counties with high rates of in-migration from the northern U.S., mortality curves parallel the mortality curves for other large southern counties. A death certificate-based case-control study of colorectal cancer involving telephone interviews of next-of-kin of 1,100 cases and 1,341 controls was conducted in these Florida retirement counties to assess whether there is a rapid reduction in risk on migration to the South and to explore possible causes, such as diet or sunlight.

5. A two-year, methodologic case-control study of colorectal cancer and diet was conducted at Walter Reed Army Medical Center, National Naval Medical Center, and George Washington University Hospital. The study focused on potential diet-related biochemical markers of colorectal cancer risk; namely, fecal mutagens, fecal bile acids, and fecapentaenes (a highly genotoxic class of fecal mutagens), as well as serum nutrient levels. Study subjects were repeatedly interviewed regarding recent diet; and multiple blood and stool samples were taken during diagnostic workup, surgery, and recovery.

6. A methodologic case-control study of colorectal cancer in relation to fecal bile acids and neutral steroids has been initiated, using 120 stored fecal samples from the fecal mutagen study described above.

7. A multi-center case-control study of 500 women with endometrial cancer is underway. An equal number of community controls and women hospitalized for hysterectomy for benign conditions will serve as comparison subjects. The dietary interview is designed to measure intake of all major nutrients, with a special emphasis on fat. To explore the role of obesity, height, weight, relative weight, and physical activity at various ages are being ascertained, and anthropometric measurements taken. Blood samples will enable a battery of hormone assays to be conducted so that the interrelationships of obesity, diet, hormones, and cancer risk can be evaluated. In one particular study center, fat patterns will be further investigated in the cases and hysterectomy patients with a methodologic study of fatty acid profiles carried out on plasma, red blood cells, cheek cells, abdomen and arm aspirates, and surgical abdominal fat, and with serologic determinations of cholesterol, triglycerides, and lipoproteins.

8. In the population-based case-control study of ovarian cancer in Shanghai, China, described in project Z01CP05526-03 EEB, usual adult intake of common Chinese foods was quantitatively assessed.

9. A dietary component focused on micronutrients postulated to be involved in the etiology of cervical cancer was added to the U.S. case-control study of invasive and in situ cervical cancer, described in project Z01CP05526-03 EEB. Food frequencies and a history of vitamin supplement use were used to estimate the usual adult intake of carotenoids, vitamin A, vitamin C, and folacin. In addition, information was collected on the use of vitamin supplementation

during pregnancies since folacin depletion may occur during this time. To complement the dietary interview, blood samples were collected six months after completion of treatment to measure serum levels of retinol, carotenoids, tocopherols, vitamin C, folacin, and selenium and red blood cell folacin.

10. The case-control study of in situ cervical cancer conducted in Australia, and described in project Z01CP05526-03 EEB, included a quantitative food frequency questionnaire to assess carotenoids and retinol in the diet. Plasma levels of total carotenoids and beta-carotene were also measured.

11. A dietary component, with an orientation similar to that of the U.S. cervical cancer study, was part of the Latin American study of invasive cervical cancer, described in project Z01CP05526-03 EEB. The influence of diet, as well as serum levels of retinol, carotenoids, tocopherols, and folacin will be examined.

12. The population-based case-control study of vaginal and vulvar cancer, described in project Z01CP05526-03 EEB, contained a dietary section and laboratory component oriented toward the micronutrients and dietary patterns hypothesized to be involved in cervical cancer etiology.

13. In the case-control study of tumors that occur excessively in blacks, described in project Z01CP05526-03 EEB, diet will be extensively evaluated with emphasis on macronutrients, micronutrients, food groups, and cooking practices. Selected micronutrients will be measured in serum collected from the patients with prostate cancer or multiple myeloma, and from the controls.

14. In collaboration with the National Institute of Standards and Technology (NIST) methodologic studies are being carried out to assess vitamin C and carotenoids in serum. The vitamin C work focuses on stabilizing this micronutrient during field collection and long-term storage of serum samples. It also examines the validity and reproducibility of a high performance liquid chromatography assay method. The carotenoid work focuses on the quantitative measurement of the major carotenoids in human serum and the variation in these levels in the U.S. population.

15. Questions about usual adult frequency of consumption of beer, wine, and hard liquor were added to a population-based incident case-control study of lung cancer in six high-risk areas of New Jersey. Interviews were completed for 763 cases and 900 controls.

16. A large multi-center population-based case-control study of oral and pharyngeal cancer was completed by the Biostatistics Branch. A total of 1,065 cases and 1,182 controls or their next-of-kin were interviewed with a food frequency questionnaire to assess intake of the major sources of carotenoids, vitamin C, and dietary fiber as well as the overall pattern of the diet.

17. Data were analyzed from a case-control interview study of malignant mesothelioma in Louisiana, which gathered information on usual diet and on lifetime occupational exposure to asbestos. Thirty-seven patients with malignant mesothelioma of the pleura or peritoneum were matched to controls according to age, sex, race, and factors related to case ascertainment.

18. In cooperation with the National Institute on Aging, other NIH Institutes, and the National Center for Health Statistics (NCHS), we attempted to trace and re-interview, by proxy if necessary, the 14,407 adults examined 8-14 years earlier in the National Health and Nutrition Examination Survey I (NHANES I). Hospital records and death certificates were collected. Approximately 93% of the cohort was successfully traced. To facilitate future use of this cohort, we incorporated into the re-interview 1) additional questions about the major risk factors for the common cancers not included in the original interview, and 2) an expanded dietary section to complement the single 24-hour dietary recall originally administered.

Major Findings:

In the case-control study of breast cancer within the BCDDP, risk increased with progressive measures of height. The effect of weight independent of height was evaluated using indices of relative weight, which was a risk factor among women over 50 years of age and those having undergone a natural menopause. In contrast, an inverse association between relative weight and breast cancer was seen for younger women; this was restricted to the smaller tumors and probably reflects a detection bias.

In the case-control study of colorectal cancer in Florida retirement counties, preliminary results indicate that increasing years of Florida residence for migrants from the north is not associated with decreasing risk of disease. However, the younger the age at migration to Florida, the lower the risk of colorectal cancer in both men and women, with the risk of those migrating at 36 to 65 years of age and at 66 years or older being 1.3 and 1.7, respectively, compared to the risk of those migrating prior to age 36.

Results from the study of fecal mutagens, diet, and colorectal cancer show a striking decrease in fecapentaene excretion among cases compared to controls that cannot be explained by the effects of diagnostic workup or bleeding. An autopsy study showed that excreted values are equivalent to intra-colonic measurements. These results fail to support a genotoxic role for fecapentaenes in the etiology of colorectal cancer. Most mutagenicity in the 718 collected samples could be explained by fecapentaene content. Non-fecapentaene TA 98 mutagens were significantly elevated in cases compared to controls, with an estimated relative risk of 4.4. Possible dietary origins of this mutagenicity, including cooked meats, are being investigated.

In the case-control study of ovarian cancer in Shanghai, the risk of epithelial ovarian cancer increased with the intake of fat from animal sources, but not with fat from plant sources. After adjustment for socioeconomic status and other ovarian cancer risk factors, women in the highest quartile of animal fat consumption had 1.8 times the risk of those in the lowest quartile. After adjustment for animal fat intake, calories and protein intake had minimal effects on risk. Total vegetable intake was found to be somewhat protective, but the mechanism of action was unclear.

In the case-control study of *in situ* cervical cancer in Australia, women in the lowest quartile of carotenoid, vitamin C, or folacin intake had approximately twice the risk of those in the highest quartile, although the trend was

significant only for vitamin C. Retinol intake was not predictive of risk. Among the food items, salad vegetables and fruit juices were the most protective. The levels of total carotenoids and beta-carotene in the plasma were both inversely associated with risk, with women in the lowest quartile of beta-carotene having 5 times the risk of women in the highest quartile.

In the case-control study of cervical cancer in the U.S., women in the highest quartiles of intake of carotenoids, vitamin A, vitamin C, and folacin had adjusted relative risks of invasive squamous cell cervical cancer comparable to women in the lowest quartiles, although their micronutrient intake was estimated to be 3-4 times as high. Risk was not affected by increased consumption of vegetables, dark green vegetables, dark yellow-orange vegetables, legumes, or fruits, or by high intake of the basic food groups. These generally negative findings stand in contrast to previous epidemiologic studies, which suggest these micronutrients are protective; the discrepancy is not readily explained by bias, uncontrolled confounding, or inadequate power.

In the case-control study of lung cancer among white men in New Jersey, the risk associated with drinking any type of alcoholic beverage compared to nondrinkers was minimal (RR=1.1). Neither wine nor spirits was associated with risk of lung cancer at any level of consumption. Heavy beer consumption was associated with elevated risk, but only among those who drank beer exclusively and could be due to uncontrolled confounding by some aspect of lifestyle.

In the case-control study of oral and pharyngeal cancer, the analysis of diet in the white males and females showed a protective effect of fruits, and some vegetables (those usually eaten raw). No nutrient examined (vitamin C, vitamin E, vitamin A, carotenoids, fiber, folacin) could explain this finding. Nitrites, coffee, and low consumption of various minerals (such as iron) and B-vitamins were not associated with increased risk. Preliminary analyses of the black males and females show many similarities, but vegetables appear to be more protective. Preliminary analyses of vitamin supplement data in both the whites and blacks show independent protective effects for some vitamins.

In the case-control study of malignant mesothelioma of the pleura and peritoneum conducted in Louisiana, the cases reported less frequent consumption of homegrown produce, cruciferous vegetables (p=.005), and all vegetables combined. An estimate of carotenoid intake was also significantly lower among cases. This reduction in risk with vegetable intake for a non-epithelial tumor could not be explained by differential asbestos exposure.

The relationship of anthropometric variables to risk of breast cancer was examined in the NHANES I cohort. Women who developed breast cancer were taller and had greater frame size (elbow width) than non-diseased women. However, body size defined by weight, relative weight, or skinfold measurements was not associated with increased risk. The positive association of stature and frame size to breast cancer risk suggests that early nutrition may play an etiologic role.

The relation between serum cholesterol and cancer was also examined in the NHANES I cohort. Men in the lowest cholesterol quintile had nearly twice the incidence and mortality of those in the highest quintile. Among women a

similar relation was seen for cancer mortality, but not for cancer incidence. The inverse cholesterol-cancer relationship in men was present for determinations made 6 or more years before cancer diagnosis, suggesting that lowered serum cholesterol may not simply be a result of preclinical disease. Analysis by site revealed inverse associations for cancers of the lung, rectum, bladder, and pancreas (but not colon) among men; and for cancers of the lung, bladder, pancreas, and cervix and leukemia (but not colon) among women. Thus, lowered cholesterol as a risk factor was primarily restricted to smoking-related cancers, a finding that persisted after adjustment for smoking.

The relation between serum vitamin A measurements made at baseline examination and subsequent development of prostate cancer was examined in the NHANES I Follow-up Study. The mean level of serum vitamin A was significantly lower ($p<0.001$) in prostate cancer cases than in non-cases. Individuals in the lowest quartile of serum vitamin A had a relative risk of 2.4 compared to those in the highest quartile. Since the risk associated with low levels of serum vitamin A did not decrease with increasing time until diagnosis, metabolic effects of early disease are not a likely explanation of these results.

Publications:

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Brock KE, Hoover RN, Hensley WJ. Plasma cholesterol and the in situ cervical cancer: an Australian case-control study [Letter to the Editor]. J Clin Epidemiol 1989;42:87-9.

McLaughlin JK, Gridley G, Block G, Winn DM, Martin S, Schoenberg JB, Greenberg RS, Stemhagen A, Austin DF, Ershow AG, Blot WJ, Fraumeni JF Jr. Dietary factors in oral and pharyngeal cancer. JNCI 1988;80:1237-43.

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Schiffman MH, Bitterman P, Viciana AL, Schairer C, Russell L, Van Tassell RL, Wilkins TD. Fecapentaenes and their precursors throughout human bowel: results from an autopsy study. Mutation Res 1988;208:9-15.

Schiffman MH, Felton JS. Fried foods and the risk of colon cancer. Am J Epidemiol (In Press).

Schiffman MH, Pickle LW, Fontham E, Zahm SH, Falk R, Mele J, Correa P, Fraumeni JF Jr. A case-control study of diet and mesothelioma. Cancer Res 1988;48:2911-15.

Schiffman MH, Van Tassell RL, Andrews AW, Daniel J, Robinson A, Smith L, Daniel J, Hoover RN, Weil R, Rosenthal J, Nair PP, Wilkins TD. Case-control study of colorectal cancer and fecapentaene excretion. Cancer Res 1989;49:1322-6.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05400-06 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Epidemiology of Human 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, Viral Epidemiology Section	EEB	NCI
Others:	R.J. Biggar	Coordinator, International AIDS	EEB	NCI
	J.J. Goedert	Coordinator, AIDS Working Group	EEB	NCI
	S.Z. Wiktor	Medical Staff Fellow	EEB	NCI
	A. Manns	Biotechnology Fellow	EEB	NCI
	P.H. Levine	Senior Investigator	EEB	NCI
	D.J. Caussy	Fogarty Fellow	EEB	NCI
	A. Kramer	Guest Researcher	EEB	NCI

COOPERATING UNITS *(if any)*
U.W. Indies, Kingston (B. Hanchard); Caribbean Epidemiology Centre (C. Bartholomew); Research Triangle Institute (D. Waddell, A. Levin); Program Resources, Inc. (D. Waters, J. Drummond); U. of Alabama (G. Shaw)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Viral Epidemiology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
10	9.0	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 diseases. Human T-lymphotrophic virus-I (HTLV-I) is linked to adult T-cell leukemia (ATL) and tropical spastic paraparesis. Human immunodeficiency virus, (HIV) the etiologic agent of the acquired immunodeficiency syndrome (AIDS), is associated with Kaposi's sarcoma, Hodgkin's and non-Hodgkin's lymphoma and possibly hepatocellular carcinoma. Results of our studies document the spectrum of ATL and modes of spread of HTLV-I by maternal-to-child transmission, hetero- and homosexual contact, and via blood transfusion and needle sharing among drug abusers. An indirect etiologic mechanism suggested for HTLV-I in B-cell chronic lymphocytic leukemia (B-CLL), and for HIV in Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma. Our HIV research has focused on cohorts at high-risk for AIDS followed longitudinally since the very beginning of the AIDS epidemic. Results have documented major modes of transmission of HIV in homosexual men, in hemophiliacs, and in drug users and their heterosexual partners, and from mother to offspring. The natural history of progression, the predictors and risk, and the incidence of various outcomes have been defined. Low T-helper cell counts are predictive of AIDS risk and may contribute to heightened transmission of HIV. An immunogenetic marker appears to be associated with heightened AIDS risk. With the recent discovery of human herpes virus -6 our interest in DNA tumor viruses has also been revitalized. Biochemical epidemiologic studies to investigate the possible role of oncogenic DNA viruses in HIV-1 related malignancies are planned.

PROJECT DESCRIPTION

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

W. A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
R. J. Biggar	Coordinator, International AIDS	EEB	NCI
J. J. Goedert	Coordinator, AIDS Working Group	EEB	NCI
D. L. Mann	Head, Immunogenetics Section	LVC	NCI
R. C. Gallo	Chief	LTCB	NCI
S.Z. Wiktor	Medical Staff Fellow	EEB	NCI
A. Manns	Biotechnology Fellow	EEB	NCI
D.J. Caussy	Fogarty Fellow	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
P. H. Levine	Senior Investigator	EEB	NCI
E. Maloney	Statistician	EEB	NCI
D. Reidel	Epidemiologist	EEB	NCI
A. Kraemer	Guest Researcher	EEB	NCI

Objective:

The objective of the Viral Epidemiology Section is to generate and test hypotheses concerning the role of pathogenic human viruses in the etiology of cancer and to expand our knowledge of the AIDS epidemic, with a particular focus on cancer.

Methods Employed:

Studies undertaken by the Viral Epidemiology Section involve a series of research approaches. Cross-sectional surveys and descriptive case series are employed to provide initial information on the distribution of virus exposure and the nature of related diseases. A major tool for analysis is the prospective cohort study which provides information on the natural history of infection, the frequency of disease occurrence resulting from exposure and the cofactors which modify risk. To analyze specific risk factors, case-control studies are employed defined on the basis of risk factors for infection or outcome. A variety of biochemical markers are utilized to define intermediate outcomes or markers of high risk.

Major Findings:

PROJECT 1: Human T-cell Lymphotrophic Virus-I (HTLV-I)

The discovery of the first human retrovirus, HTLV-I, by the Laboratory of Tumor Cell Biology (LTCB) of the NCI has given new impetus to the hypothesis that viruses cause 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. To accomplish this objective, the Viral Epidemiology Section of the Environmental Epidemiology Branch has developed a series of projects in the

United States and internationally to explore etiologic relationships between HTLV-I and suspected disease outcomes. To support these activities, a series of research contracts have been established with the University of West Indies at Kingston, Jamaica; the Caribbean Epidemiology Research Center, Port-of-Spain, Trinidad; Gorgas Memorial Institute, Panama City, Panama; and the Kuakini Medical Center in Honolulu, Hawaii.

Adult T-cell Leukemia

A case-control study of adult T-cell leukemia (ATL), established in Kingston, Jamaica in January 1984 and in Port-of-Spain, Trinidad in February 1985, completed enrollment of over 120 cases of ATL in February 1989. Preliminary analysis has documented a 35-fold increase in risk for ATL among persons seropositive for HTLV-I. A current thrust of this project is to apply new tissue typing approaches to clarify the T-cell phenotype of cases. In addition, the technique of polymerase chain reaction will be applied to search for virus-positive, antibody-negative ATL cases.

The molecular analysis for HTLV-I of Jamaican non-Hodgkin's lymphoma cases utilizing conventional molecular hybridization approaches documented the presence of integrated HTLV-I viral DNA in all antibody-positive cases and its absence in negative cases. We modeled the incidence of ATL in the Jamaican population and found that age-specific male and female rates are similar, while the pattern of disease in relationship to age-specific infection rates suggests that early life exposure is most important for subsequent risk for ATL.

Surveys of adult non-Hodgkin's lymphoma to search for HTLV-I-associated ATL have been undertaken in several geographic locales. In the United States, an ATL registry has been developed for categorizing cases previously identified, to enroll new cases referred to the NCI for evaluation, and to record features of cases reported in the literature. Thus far, 111 cases have been recorded by the Registry and 83 of these have been confirmed using an algorithm recently developed by the EEB. A systematic set of criteria for documenting which cases represent typical versus atypical ATL were established and a spectrum of disease subtypes characterized. This finding points to the difficulty of correctly classifying cases in a non-endemic area for HTLV-I. The previously identified pattern of U.S. cases was confirmed. Specifically, ATL occurs most often among persons of African ancestry, either born or with links to the southeastern U.S., or among migrants to the U.S. from viral endemic areas of the world, particularly the Caribbean basin, but also among Japanese Americans with links to southern Japan. An extension of a study which characterized a cluster of ATL in Brooklyn, New York has included a screen for HTLV-I in the community, suggesting the virus most often affects families originating from North and South Carolina.

A survey in Panama has documented a paucity of cases despite elevated rates of seropositivity in the population at risk. These cases share common features with ATL from the region, but the proportion is much lower than that reported from Jamaica and Trinidad. Surveys in other areas previously suspected to have significant HTLV-I seroprevalence were developed in Ghana, Nigeria, and Papua, New Guinea.

New Guinea. Less than one percent of Ghanaians were found to be seropositive, suggesting the high prevalence reported in previous studies was based in large part on false positive reactivity.

Tropical Spastic Paraparesis

Recently, a link of HTLV-I to a demyelinating neurologic condition, tropical spastic paraparesis (TSP), has been reported. In conjunction with collaborators from the National Institute of Neurological Disorders and Stroke (NINDS) and Jamaican and Trinidadian collaborators, we are initiating an analytic case-control study of TSP utilizing a questionnaire patterned after our questionnaire utilized to study ATL. This parallel study seeks to define similarities and differences between TSP and ATL which may provide clues to latency and risk factors for these HTLV-I-related diseases. As part of this protocol, we are evaluating the hypothesis that different immunogenetic factors predispose to these diseases. In Panama, four incident cases of TSP were ascertained nationwide over 18 months compared to less than 1 case per year of ATL. Cases often had onset of symptoms years before seeking medical attention emphasizing that incidence based estimates of disease occurrence may be biased by the chronic course of symptoms. Based on data from our studies of ATL and TSP we hypothesize that the shorter latency from exposure to disease occurrence in TSP may be a reflection of an indirect immune mediated mechanism of disease occurrence. Based on these four cases an intensive search for more cases was initiated in Indian populations with a documented increase in seroprevalence.

Foodhandler Study

In Jamaica, the cross-sectional seroprevalence survey of 13,500 food service employees (foodhandlers) is the mainstay of our future targeted epidemiologic studies. Analysis of these data was delayed while our HTLV-I testing was upgraded but is now complete and manuscript preparation is in progress. The major findings include: a) a marked female excess in prevalence for all adult age groups; b) generally uniform geographical distribution of HTLV-I prevalence across the island of Jamaica, except for lower rates linked to residence at higher elevation; and c) when age is controlled, there is no association between a woman's parity (cumulative number of pregnancies) and her likelihood of being seropositive. However the parity link is complex since associations are seen in the younger age groups which disappear in older age groups, suggesting that age determined behavior influences subsequent HTLV-I risk. Further investigation is ongoing.

Phase two of the foodhandler survey is a nested case-control study of risk factors for seropositivity. Two hundred fifty healthy seropositives were frequency-matched by age, sex, and locale of current residence with an equal number of seronegatives. Trained research nurses administered a detailed questionnaire modeled after the ATL case-control questionnaire covering medical and sexual history, residence, occupation, diet, and lifestyle. Blood and stool specimens were obtained for blood smear, serology, lymphocyte preservation, and examination for ova and parasites. In addition, a physical examination designed as a screening tool for ATL and TSP was performed by the nurses. Begun in January 1987, the field component of this phase is now

complete. Of interest is the fact that among the first 150 seropositives to be screened, five had neurologic symptoms or signs, and one of these has been confirmed as a case of TSP.

Hepatitis Cohort

In Trinidad and Tobago, an occupationally-based cohort of 1,729 persons had been assembled for a study of hepatitis prevalence in 1982. Seroprevalence was higher on the small island of Tobago (11/151=11.9%) than on the larger island of Trinidad (35/1,575=2.2%). The use of an outdoor water supply and an outdoor toilet were both correlated with HTLV-I seropositivity on Tobago, suggesting that lower socioeconomic status may be linked to the higher rates on the small island. HTLV-I seropositivity was correlated with the presence of antibodies to hepatitis-B, which appeared to be a surrogate for male-to-female sexual transmission.

Barbados Cohort

In 1972, sera were collected by Dr. Alfred Evans (Yale University) in a population-based household survey of two health districts in Bridgetown, Barbados. We recently tested sera from this collection for HTLV-I. Overall, HTLV-I prevalence was 4.3% (43/1,012), with an age-specific increase and higher rates in females (5.7%) than in males (2.2%). The age dependent rise in seroprevalence has a pattern identical (but at a lower rate) to the curve observed in the foodhandler survey in Jamaica, arguing that the age-dependent rise is not a result of a cohort effect since we would have expected higher rates to have been shifted to a younger age stratum in the 1972 survey. Data on results from the fluorescent treponemal antibody (FTA) test for syphilis were available for the cohort. A stronger correlation between positive FTA and antibodies to HTLV-I was observed for females (odds ratio=4.1, 95% CI=1.7, 9.7) than for males (odds ratio=2.6, 95% CI=0.5, 13.8). This is evidence in favor of preferential sexual transmission from males to females rather than from females to males. Perinatal transmission of HTLV-I was suggested by household clustering of antibody and the fact that seropositive children were more likely to have seropositive mothers than seronegative children, a pattern that was reported from Japan. There was no evidence in support of vector-borne transmission. We hope to reevaluate this 16-year-old cohort with questionnaires, blood samples, and physical examinations during 1989 to address the important issues of interval seroconversion and disease outcome.

Japan-Hawaii Cancer Study Cohort

Serologic analysis of a cohort of Hawaiian men from the Japan-Hawaii Cancer Study showed high rates of seropositivity among Japanese American residents with links to the viral endemic areas of Japan, Okinawa. Preliminary data from a follow back to this cohort suggest that rates of infection may be declining in the next U.S.-born generation, an observation being evaluated by an analytic case-control study. Household transmission appears to be linked to male-to-female, sexual transmission. There is a correlation between higher HTLV-1 virus antibody titer in the husband and higher rates of infection in female spouses. Genetics may also play a role. Our collaborators in Hawaii have recently identified a second member of the cohort who has developed ATL. These

cases are seropositive brothers who were diagnosed with ATL seven years apart and whose documented antibody positivity antedated their development of ATL by 7 to 15 years.

Sexual Transmission

Sexual intercourse was postulated to be an important mode of transmission of HTLV-I by Japanese investigators early in the epidemiological investigations of the virus.

The prototype of our studies of sexual transmission had its field phase in Jamaica where 2,000 sequential patients at sexually-transmitted disease (STD) clinics in Kingston and Montego Bay were enrolled when they presented for a new episode of STD. Serum and questionnaire data on sexual behavior were obtained from all subjects. After adjusting for age, the female prevalence was significantly greater than that of female foodhandlers who are felt to be more representative of the general population. For females, number of lifetime partners and history of syphilis and/or positive syphilis serology were correlated with positive HTLV-I antibody. For males a positive syphilis serology and history of ulcerative genital lesions suggests that these factors may be involved in promoting female-to-male transmission.

In Trinidad, a study of heterosexual patients at the local STD clinic has been completed. It was initially intended to be similar to the study in Jamaica, but the finding of higher prevalence against HIV (23/747, or 3%) than against HTLV-I (15/747, or 2%) in the Trinidad STD clinic population has led us to reevaluate our approach. First, we need to ascertain by means of follow-up interviews that the HIV seropositives were indeed exclusively heterosexual. A nested case-control or case-contract study of HIV risk factors in this heterosexual group is planned.

We have also undertaken studies of homosexual and bisexual men in both Trinidad and Jamaica. In Trinidad, HTLV-I and HIV seroprevalence rates were 15% and 40%, respectively, compared to 2.4% and 0.19% in a more general population survey. In Jamaica, HTLV-I and HIV seroprevalence were 5% and 10%, respectively, compared to 3% and 0.1%, respectively, in the foodhandler cohort. The studies found evidence that the high HTLV-I prevalence among these males was due to transmission by homosexual intercourse, and that duration of homosexuality, number of sexual partners, and history of gonorrhea infections were risk factors. In contrast, the strongest risk factor for HIV infection was sexual contact with American men. The risk factors usually associated with HIV infection in U.S. homosexual men were more difficult to detect, due in part to the small numbers of seropositives in these two studies. A follow-up of the 1983-84 Trinidad homosexual cohort for HIV and HTLV-I seroconversion, and for incidence of AIDS, suggests that men co-infected with both viruses are at greater risk of developing AIDS.

We have also examined the hypothesis that homosexual men in the U.S. have an elevated prevalence of HTLV-I. From the Los Angeles site of the Multicenter AIDS Cohort Study (MACS) 1,279 sera from gay men, plus 316 sera from homosexual

men in New York City, Washington D.C., or Hawaii, were tested for HTLV-I antibodies. Only one man (0.06%) was seropositive, suggesting that HTLV-I has not been introduced into these groups.

Maternal to Child Transmission

Data collection has been completed on two preliminary surveys of maternal-infant HTLV-I transmission in Jamaica through collaboration with the Department of Child Health of the University of West Indies. Serial serum samples were collected from 600 infants for a study of measles vaccination efficacy. Testing for HTLV-I antibodies has revealed 7 HTLV-I positive children. Family studies of the 7 seropositive and 14 matched seronegative children revealed that all positive children have seropositive mothers. In another retrospective pilot study in Kingston, Jamaica, 74 HTLV-I positive pregnant females and their offspring were followed to determine the frequency of HTLV-I antibodies among their offspring. Of all offspring of seropositive mothers, approximately 20% appear to be seropositive. An expanded survey to ascertain the route of transmission, specifically the role of breast-feeding, and to identify the immunologic effects of perinatal HTLV-I infection is in the field phase of data and sample collection.

Transfusion Transmission of HTLV-I

The Jamaican Blood Transfusion Service, sponsored by the Ministry of Health, serves as the major source of blood and blood products for the country of Jamaica. Over 54% of the island's blood originates from the Service's Main Center in Kingston, with 12,000 units collected per year. This center serves as the site of donor screening for this study, and recipients of blood units are in-patients at Kingston urban hospitals. For the study all consecutive donors at the Main Center and University of the West Indies Hospital are screened for HTLV-I antibody by the NCI laboratory in Frederick with experimental assays prior to FDA licensure. Pre-transfusion specimens were frozen for later analysis. In cases where blood units are not intercepted before transfusion, recipient pre- and post-transfusion samples are screened. Individuals with positive pre-transfusion samples were followed to evaluate the effect of re-exposure on antibody titer, and are being analyzed separately from those who were pretransfusion negative. Controls, matched to newly-exposed cases by age, sex, and hospital, who received negative donor blood during the period of the study are being followed in an identical fashion. Serial serum samples and questionnaire data are being collected on a monthly basis for at least six months following transfusion.

Screening of blood donors commenced on May 29, 1987 and ended in May 1988. Seroprevalence is 2.6% in donors. Total enrollment of eligible recipients of positive units and recipient/controls approaches 100, with 50 in each group. All have had index visits and 68% have had at least one monthly interval visit. A minimum of 45% of recipients of HTLV-I positive blood units have seroconverted after a median time of 50 days. No recipients of negative blood units have seroconverted. Whole blood and cell components of blood but not cell free materials are linked to seroconversion. Longer shelf life is associated with decreased seroconversion. No clinical syndrome has emerged in

association with HTLV-I infection. Antibody response in seroconversion suggests that while patterns vary from case to case that core antibody and envelope antibody positivity emerge almost simultaneously.

HTLV-I in Drug Abusers

In 1985 a serologic survey of parenteral drug abusers in New Orleans documented a high rate of HTLV-I/II seropositivity particularly among blacks. Contrary to expectation when these samples were examined for virus type by polymerase chain reaction by Dr. George Shaw, the majority were HTLV-II and not HTLV-I. This finding reveals for the first time a reservoir of HTLV-II infection and follow-up is now underway to carefully evaluate for clinical outcomes including cancers linked to HTLV-II.

PROJECT 2: HIV and AIDS

Hemophiliacs and Their Female Sexual Partners

First evaluated in 1982, studies of hemophiliacs and their female sexual partners constitute the largest of the HIV studies. A multicenter prospective cohort of 1,219 subjects with hemophilia or related disorders has been studied to define the rates, markers and cofactors of HIV infection and AIDS. By testing previously frozen serum samples for HIV antibodies, this cohort is the world's largest with documented incident HIV infections. By dating HIV infection both by midpoint calculations and by maximum likelihood hazard functions, we demonstrated that the HIV epidemic appeared in hemophiliacs in late 1978, spread rapidly during the early 1980s, and ended by 1986. Subjects with severe hemophilia A became infected earlier and at a much higher rate, eventually 77%, than those with other clotting disorders. The AIDS incubation distribution was defined, and potential cofactors, such as race; type and severity of hemophilia; and dose of clotting-factor concentrate, did not affect AIDS incidence among HIV-infected hemophiliacs. A number of laboratory markers identified those at highest risk of AIDS, particularly low CD4-cell counts, p24 antigenemia, lack of anti-p24, and circulating interferon. The interactions of age at seroconversion with these markers suggested that early immunodeficiency occurs at a much higher rate in older (age 35-70) hemophiliacs and that AIDS occurs at a low rate in young hemophiliacs even after the appearance of advanced immunodeficiency. These findings have substantial implications for clinical care, investigational drug trials, and backcalculation to estimate the size and trend of the HIV epidemic (see below).

In a subset of the hemophiliacs at one center, the predictive value of p24 antigen, anti-p24, and anti-gp120 were compared to T4 (CD4) cell counts. The results demonstrated that p24 antigen and low T4 cell counts are strong predictors of AIDS. Detection of p24 antigen is highly specific and complementary to the greater sensitivity of low T4 cell counts. In those subjects with a T4 count < 200 cells/ul when p24 antigen appeared, two year AIDS incidence was 67%.

Female sexual partners of p24-antigenemic hemophiliacs appear to be at 3-fold to 6-fold higher risk of HIV infection than partners of non-antigenemic

hemophiliacs. Risk is also higher in partners of men with advanced immunodeficiency. The hazard rates of heterosexual transmission suggest that risk may be highest at the time of initial HIV infection in the man and also late in the course, after the appearance of advanced immunodeficiency.

Backcalculation of the HIV Epidemic

In close collaboration with the Epidemiologic Methods Section of the Biostatistics Branch, the method of backcalculation first reported by Brookmeyer and Gail has been refined, tested, and simplified. Backcalculation is the application of the AIDS incubation distribution to calculate the numbers of persons infected with HIV in previous intervals to account for AIDS cases in national surveillance. Using the incubation distribution reported by Brookmeyer and Goedert for adult hemophiliacs, the method can demonstrate both the appearance and disappearance of the HIV epidemic in U.S. hemophiliacs, with numbers infected in each interval and total number infected. The appearance and near-elimination of the HIV epidemic in homosexual men in the western-U.S. can also be observed. Preliminary results suggest that some 1.2 million persons were infected with HIV by the spring of 1988, with marked downward trends in homosexual men and marked upward trends in drug users nationwide.

Parenteral Drug Abusers

In collaboration with the National Institute on Drug Abuse, 1,766 parenteral drug users recruited from treatment programs across the United States were evaluated for prevalence of HIV and/or HTLV-I/II. Of these, 370 (21.0%) had HIV antibodies, with substantially higher rates among Blacks (33.0%) and Hispanics (20.1%) than Whites (10.3%). HTLV-I/II antibodies were noted in 189 (10.7%) of the subjects, including 19.1% among Blacks, 8.5% among Hispanics, and 4.8% among Whites. HTLV prevalence increased with older age in all racial groups but was similar in males and females. Coinfection with both viruses was noted in the expected proportion of Blacks (7.1%) but was lower than expected in Hispanics (0.5%) and Whites (0.2%), although this appeared to be attributable to geographic heterogeneity. Additional work is in progress to evaluate risk factors for infection with these retroviruses among parenteral drug users.

Mothers and Infants

This study is conducted in close collaboration with the National Institute of Child Health and Human Development, the State University of New York Health Sciences Center at Brooklyn, and the Albert Einstein College of Medicine in the Bronx, New York. Two hundred fifty pregnant women, approximately 40% of whom are HIV-infected, have given birth to approximately 150 babies. Thus far, HIV-infected women with advanced immunodeficiency have developed Pneumocystis penumonia and other opportunistic infections at a high rate, but there have been no marked increase in adverse pregnancy outcomes. Early evaluation and follow-up of the children suggest that babies of HIV-positive women compared to those of HIV-negative women, are more likely to experience delays in growth in weight, length, and head circumference. No clear HIV-related neurological syndrome could be defined in the first year of life, but neuropsychological

evaluation has suggested that both verbal and motor development may be significantly delayed.

Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30% of their offspring, with premature babies appearing to be at 3-fold higher risk than full-term babies. Remarkably, mothers who did transmit HIV to full-term babies had very low or absent antibody reactivities to gp120, the HIV envelope glycoprotein. Further laboratory characterization of this observation is in progress.

Homosexual Men

Two new analyses have been completed on the cohorts of homosexual men that we have followed since 1982. First, two potential serological markers of progression to AIDS, neopterin and ß-2-microglobulin, have been compared to CD4 counts. Presence of neopterin is clearly an independent AIDS marker, indicating a high AIDS risk some three years before diagnosis. The value of ß-2-microglobulin is clear in the year before AIDS diagnosis.

In a second analysis, the sexual activities were evaluated with respect to knowledge of one's own and one's partners' HIV status. Results indicated that risky homosexual activity had fallen markedly since 1982, but that one-third of men continued to engage in receptive anal intercourse, most without a condom or with partners of unknown HIV status. On the positive side, the findings also indicated that men almost never knowingly had sex with a partner of opposite (i.e., discordant) HIV status. A third analysis, neuropsychological abnormalities by HIV immunodeficiency status, is in progress.

Global AIDS and HIV-Infection

An international registry of has been established for persons with documented dates of HIV seroconversion in order to evaluate cofactors and trends of AIDS risk. Thirty-eight investigators from three continents have contributed 1,115 subjects for analysis. Analysis focused on the 816 subjects enrolled in prospective studies who had HIV seroconversion documented within a window of 25 months. Within the risk group, time-to-AIDS was the same in all areas and among early (pre-1985) and later seroconverters. Children with hemophilia progressed to AIDS more quickly than adults, and homosexual men progressed to AIDS more quickly than adults with hemophilia because of an excess of Kaposi's sarcoma in the former. Time-to-Pneumocystis pneumonia was similar in hemophilic and homosexual adults. Too few drug users, heterosexual partners, and transfusion recipients have been enrolled to evaluate thus far, but follow-up is continuing and additional contributions are being sought.

Related Retroviruses

We maintain an active program in collaboration with Dr. R. Gallo to isolate and characterize known retroviruses from different areas of the world in the hope that strain differences may provide a clue to the clinical variation in progression to AIDS or in "natural resistance," if such exists. We also seek to find new agents. Several lines of evidence suggest the concept that there may be several other retroviruses in some parts of the world. Their existence

and relationship to other viruses needs to be demonstrated and their relationship to human disease described. Current areas of interest are in Panama, Greece, New Guinea, Tanzania, Nigeria and parts of the United States with an increased American Indian population. In addition, we are seeking samples from persons infected many years ago to examine changes in retroviruses that have occurred over time. To do this with HTLV-I, we have arranged a collaboration with the Veterans Administration Hospital in Washington, D.C., to examine collections of sera obtained from drug abusers in the early 1970s. Such studies will also help to determine the health impact of infections, since subjects in this study can, in theory, continue to be followed through the V.A. system.

PROJECT 3: Lymphotrophic Herpes Viruses and Cancers

The well-documented relationship between Epstein-Barr virus (EBV) and both Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) served as a model for studies of a newly discovered herpesvirus, HHV-6. A potential relationship to human lymphoma was initially suggested by serologic studies identifying elevated antibody titers in several human malignancies, including Hodgkin's disease and acute lymphocytic leukemia, and the detection of viral genome in three human B-cell lymphomas. More recent case-control studies however, suggest that the elevated titers are due to disease associated immunosuppression resulting in reactivation of latent virus infection and are not of etiologic significance. Studies are now focusing on the evaluation of newly developed assays for HHV-6 antibodies to test the suggested associations between this virus, which is widely spread in all populations studied to date, and specific diseases. An investigation of an outbreak of chronic fatigue syndrome in Lake Tahoe region, allegedly linked to HHV-6 infection, is continuing because of the report of an increased incidence of cancer in the patients. A study investigating Burkitt's lymphomas from various geographic areas clarified the differences between EBV-related and unrelated tumors. EBV related tumors had more consistent chromosome translocations and Ig gene rearrangements. In a related effort, antibodies to antigens produced by another oncogenic herpesvirus, herpesvirus saimiri (a virus normally found in squirrel monkeys which produces lymphomas in owl monkeys and marmosets) was detected in several healthy animal handlers and controls, but the significance of these findings remains to be determined.

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CONTRACTS IN SUPPORT OF THIS PROJECT

RESEARCH TRIANGLE INSTITUTE (NO1-CP8-5603-00)

Title: Epidemiology Surveys for Human Retroviruses

Current Annual Level: $250,000

Person Years: 3

Objectives: To support international studies of human retroviruses and their relationship to illness.

Major Contributions: Studies are ongoing in Africa, Europe, South and Central America and the Caribbean.

KUAKINI MEDICAL CENTER (NO1-CP5-1023-00)

Title: HTLV-I in Migrant Populations in Hawaii and Okinawa

Current Annual Level: $193,450

Person Years: 2

Objectives: To determine the changes in HTLV-I in groups immigrating from a high prevalence area (Okinawa/Southern Japan) to low prevalence area (Hawaii).

Major Contributions: Analysis indicates a steady decline of HTLV-I prevalence and significant risk for transmission from husband to wife.

CARIBBEAN EPIDEMIOLOGY CENTER (NO1-CP6-1022-00)

Title: Epidemiology of Human T-cell Leukemia/Lymphoma Virus in Trinidad and the Caribbean Region.

Current Annual Level: $268,694

Person Years: 4

Objectives: To support studies in Trinidad on the relationship between HIV and HTLV-I.

Major Contributions: HTLV-I is endemic in Trinidad, and HIV was recently introduced and spreading. Coinfection results in accelerated AIDS development.

BRATON BIOTECH (NO1-CP5-1086-00)

Title: Immunologic Studies of High Risk Groups

Current Annual Level: $350,000

Person Years: 3

Objectives: To provide immunologic tests (T-lymphocyte subsets) on cohorts under study for the effects of human retroviruses and related malignancies.

Major Contributions: Ongoing evaluation of the immunologic status of homosexual men and hemophiliac patients have documented a steady decline over the past six years.

RESEARCH TRIANGLE INSTITUTE (NO1-CP6-1013-00)

Title: Support Services for Epidemiologic Studies of HTLV-III and Related Viruses.

Current Annual Level: $1,211,670

Person Years: 17

Objectives: To support retrovirus-related studies with field workers and computer facilities.

Major Contributions: Project staff have contributed to studies of nearly every major effort undertaken by the Viral Epidemiology Section.

UNIVERSITY OF GHANA (NO1-CP8-5612-00)

Title: Studies on the Epidemiology of Potentially Oncogenic and Immunosuppressive Viruses in West Africa.

Current Annual Level: $45,000

Person Years: 4

Objectives: To examine the entrance of HIV and the prevalence of other human retrovirus and to determine their relationship to human disease.

Major Contributions: Data indicate HIV entered Ghana in 1986, largely through prostitutes returning home from neighboring countries. Levels of knowledge are good and may be contributing to behavior changes to prevent further spread.

BIOTECH RESEARCH LABORATORIES, INC. (NO1-CP2-1121-00)

Title: Laboratory Support for Specimen Processing and Storage of Biological Specimens from Persons at High Risk of Cancer.

Current Annual Level: $301,538

Person Years: 6

Objectives: To provide services for organizing, aliquoting, storing and shipping specimens obtained by several sections of the Environmental Epidemiology Branch.

Major Contributions: This repository has received tens of thousands of samples annually and has processed them efficiently.

UNIVERSITY OF THE WEST INDIES (NO1-CP3-1006-00)

Title: Epidemiology of HTLV-I in Jamaica

Current Annual Level: $311,416

Person Years: 5

Objectives: To undertake in-depth surveys of HTLV-I in an endemic area.

Major Contributions: Studies of over 15,000 persons have provided a complete profile of the transmission and distribution of HTLV-I. Data about the health risks of HTLV-I infection are in progress.

GORGAS MEMORIAL INSTITUTE (NO1-CP3-1015-00)

Title: Epidemiology of HTLV in Panama

Current Annual Level: $150,000

Person Years: 3

Objectives: To characterize patterns of HTLV occurrence and associated diseases.

Major Contributions: Project has identified a focus of HTLV-I or related virus in isolated Indian populations which may explain discrepancy between low ATL and high TSP rates.

RESEARCH TRIANGLE INSTITUTE (NO1-CP8-5649-00)

Title: Support Services for Retrovirus Epidemiology and Natural History in Hemophiliacs and Their Sexual Partners

Current Annual Level: $500,000

Person Years: 8

Objectives: To support HIV natural history studies in hemophiliacs.

Major Contributions: Study has identified cofactors for age and provided estimates of AIDS incubation distribution.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05526-03 EEB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Analytical Investigations of Selected Issues in Human Cancer

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

PI:	L.A. Brinton	Chief, Environmental Studies	EEB	NCI
Others:	K.P. Cantor	Epidemiologist	EEB	NCI
	G. Gridley	Statistician (Health)	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	C. Schairer	Statistician (Health)	EEB	NCI
	M.H. Schiffman	Clinical Investigator	EEB	NCI

COOPERATING UNITS *(if any)*
28 BCDDPs;Gorgas Mem Lab (W Reeves);Johns Hopkins Univ (R Kurman, S West);NY Health Dept (P Nasca);IL Cancer Council (K Mallin);3 Kaiser Med Ctrs (A Glass, G Friedman, W Finkle);Mayo Clinic (J Melton);Chin Acad Med Sci (J-Y Li).

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Environmental Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
8.6	6.6	2.0

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. 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 prevalence of the exposure or the need to detect an effect at low levels of exposure). A major emphasis within this project area has been on defining the etiology of female tumors. In many of these studies, as well as in selected others, attempts have been made to assess exposures through interdisciplinary approaches. Studies completed within the last year have assessed the importance of parenchymal patterns to subsequent breast cancer risk, type-specific papillomaviruses to cervical abnormalities, a variety of risk factors for ovarian cancer in both high and low-risk areas, reproductive and contraceptive factors related to risk of trophoblastic diseases, and combination estrogen and progestin treatment as a risk factor for breast and endometrial cancers.

PROJECT DESCRIPTION

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

L.A. Brinton	Chief, Environmental Studies	EEB	NCI
K.E. Brock	IRTA Fellow	EEB	NCI
K.P. Cantor	Epidemiologist	EEB	NCI
G. Gridley	Statistician (Health)	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
R. Herrero	Visiting Fellow	EEB	NCI
A. Hildesheim	CEBTP Fellow	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
C.J. Jones	Staff Fellow	EEB	NCI
C. Schairer	Statistician (Health)	EEB	NCI
M.H. Schiffman	Clinical Investigator	EEB	NCI
X.O. Shu	Visiting Fellow	EEB	NCI
S. Sturgeon	CEBTP Fellow	EEB	NCI
R.G. Ziegler	Nutritional Epidemiologist	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 in-depth evaluations can be most efficiently carried out. (3) To design, conduct, and analyze these studies intensively.

Methods Employed:

Investigations of Female Tumors

1. A case-control study within the context of a multicenter breast cancer screening program, the Breast Cancer Detection Demonstration Project (BCDDP), involving over 10,000 interviews among women with either breast cancer, benign breast disease or no breast abnormalities, enabled a variety of newly emergent etiologic hypotheses to be evaluated.

2. In conjunction with the BCDDP case-control study, an investigation to evaluate the temporal effects of parenchymal patterns on risk of breast cancer was completed. This study focused on 266 women whose breast cancer was detected on the fifth annual screening examination, and on matched controls. Mammograms from the first, fourth, and fifth screening examinations were read blindly by Dr. John Wolfe (originator of the parenchymal pattern classification system), allowing the concordance of patterns between examinations, as well as the predictability of patterns for subsequent breast cancer, to be assessed in relation to information on standard breast cancer risk factors.

3. A follow-up study of over 60,000 participants in the BCDDP is being continued. Included for study are all women with breast cancer or benign breast disease detected during screening, as well as a sample of normal volunteers. The addition of dietary and anthropometric data to the

questionnaire will allow these factors, as well as others, to be prospectively assessed in relation to a number of outcomes.

4. A case-control study of endometrial cancer (described in detail in Z01CP05128-10 EEB) is underway in five different study areas. Although a major emphasis is on nutritional exposures, the study also will provide the opportunity to evaluate several emergent hypotheses for this tumor, including the roles of added progestin therapy, alcohol, smoking and endogenous hormones.

5. 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.

6. Data from a case-control study of 229 women with newly diagnosed ovarian cancer and an equal number of population-based controls, conducted in Shanghai, China during 1984-1986, were analyzed to determine whether risk factors in a low-risk area resemble those identified elsewhere.

7. A case-control study of 117 cases with in situ cervical cancer and 196 community controls was conducted in Sydney, Australia. Interviews focused on sexual, reproductive and medical history, as well as dietary intake, described in detail in Z01CP05128-10 EEB.

8. To determine the reasons for high rates of invasive cervical cancer, a case-control study was conducted in four Latin American countries--Colombia, Costa Rica, Mexico, and Panama. The study included personal interviews with 759 women with invasive cervical cancer and 1,532 matched controls. The husbands of sexually monogamous female subjects (204 case and 485 control husbands) were interviewed in conjunction with a clinical examination oriented toward assessing genital hygiene, circumcision status and evidence of infection. Blood samples and cervical or penile scrapings were obtained from all subjects to provide further information on the role of infectious agents.

9. A study was conducted in three hospitals in Washington, D.C. to assess how biochemical measures of smoking exposure and human papillomaviral (HPV) DNA presence interact in determining a woman's risk of cervical intraepithelial neoplasia. A total of 3,188 women were included.

10. A study to define methods for detecting papillomavirus-related DNA sequences in the cervix was conducted at Montefiore Medical Center in New York City. Patients (150) in a colposcopy clinic were sampled using an exocervical swab plus endocervical swab, or cytobrush, versus a cervicovaginal lavage.

11. An interlaboratory study of HPV detection in clinical specimens using southern blot assays was conducted with four laboratory collaborators. Forty masked identical DNA samples were distributed and the typing results compared.

12. A prospective study of early HPV infection in cytologically normal women has been initiated. A key unresolved question is the significance of HPV

infection in apparently normal women. A cohort of 25,000 pap smear screenees will be included. Cervicovaginal lavages will be frozen to permit a subsequent nested case-control study of incident atypia and dysplasia in relation to pre-morbid HPV type-specific infection. Follow-up is scheduled to last three years.

13. A case-control study to determine environmental exposures which increase the risk of vulvar and vaginal cancers was completed. Approximately 200 vulvar cancer and 50 vaginal cancer cases were ascertained over a 30-month period in Chicago and upper New York state. Subjects were interviewed and 30 ml of venous blood drawn to obtain serologic levels of micronutrients and infectious agents. In addition, fresh tumor specimens were obtained for a subset of the cases (150 women) in order to determine human papillomavirus types associated with these tumors.

14. A case-control study of 331 patients with complete hydatidiform mole, 30 with choriocarcinoma, and 622 population controls was undertaken in Beijing, China. Personal interviews enabled evaluation of a variety of risk factors for these poorly understood conditions.

15. Data were analyzed from a case-cohort study conducted in Sweden of 23,000 women who had all been prescribed non-contraceptive estrogens. All of the cases and a random sample of the cohort were administered questionnaires which elicited detailed information on estrogen exposure and selected risk factors. Based on the distribution of estrogen use in the sample, observed to expected ratios for various cancer sites in the total cohort were calculated. The case-cohort analysis was supplemented with a case-control analysis, which permitted control of confounding factors.

16. A follow-up study of 2,335 women evaluated for infertility at the Mayo Clinic during the period 1935-1964 was conducted. Information on reasons for infertility (hormonal vs. other) was evaluated in relation to subsequent cancer morbidity.

17. A number of research projects have been undertaken in collaboration with three prepaid health plans. These include 1) an evaluation of changes in breast cancer risk over time in one health plan; 2) a case-control analysis of 458 breast cancer cases and an equal number of controls to evaluate the relationship to risk of diazepam use; 3) a record-abstract, case-control study of 489 cases of histologically confirmed epithelial ovarian cancer and 604 matched controls from two plans, designed to determine the relationship of several medical conditions and procedures and therapeutic drug use to risk of this malignancy; 4) a case-control study of 124 breast cancer cases of 2,615 women with benign breast disease, where available pathology slides will enable evaluation on subsequent cancer risk of the interaction of hormone use and a dysplasia index; and 5) a nested case-control study of HPV infection in relation to progression of cervical intraepithelial neoplasia, using stored cytologic specimens and in situ DNA-DNA hybridization methods for HPV types 16 and 18.

Other Investigations

18. 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, residential history, sources of drinking water, fluid intake, 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.

19. A large study of tumors that occur excessively among blacks is underway 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 incidence rates; and (3) to use laboratory data to relate risk to certain biochemical indicators (e.g., hormones and trace metals), 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 blacks and whites who are newly diagnosed over the time period 1986-1989 in hospitals located in New Jersey, Atlanta, and Detroit. Controls are being selected from the population of each of these three areas. All subjects are being administered a standardized questionnaire. In addition, blood is being drawn on a sample of prostate cancer cases and controls and on all male multiple myeloma cases.

20. 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.

21. A population based case-control study of 309 childhood leukemia cases and 619 control children was conducted in the Shanghai urban area to explore risk factors and to examine etiologic variation by different histopathologic cell types.

22. A case-control study of penile cancer in Hunan Province, China has been completed. Included were approximately 150 patients with penile cancer, an equal number of population controls, and the wives of both groups. Interviews as well as blood specimens and penile or cervical material were obtained to evaluate a variety of etiologic hypotheses, including the role of HPV.

23. In collaboration with an investigator from Johns Hopkins University, analysis of a case-control study of nasopharyngeal carcinoma (NPC) in the Philippines has been initiated. The study included 104 biopsy proven NPC cases, and matched community and hospital controls. All subjects were tested

for antibodies to Epstein Barr virus, and a questionnaire administered to obtain data on diet, occupation, Chinese ancestry, exposure to dust, smoke, chemicals and use of herbal medicines.

24. The computer-based file of Veterans Administration hospitalization records has been expanded to 4.4 million veterans discharged between July 1, 1969 and September 30, 1985. Disease cohorts have been correspondingly increased in size, giving more stable estimates of cancer risk (Standardized Incidence Ratios [SIRs]). Internal and external rates were re-computed for these comparisons. Initial cohorts of interest include patients with rheumatoid arthritis (50,660 veterans), pernicious anemia (7,524), lupus erythematosus (2,687), Sjogren's/sicca syndrome (1,857), scleroderma (2,455), acromegaly (1,212), multiple sclerosis (16,699), kidney dialysis (23,755), infectious mononucleosis (2,077), transurethral prostatectomy (169,503), splenectomy (13,874), Klinefelter's syndrome (981), cholelithiasis (89,364), and cholecystectomy (75,607). In addition, a nested case-control medical abstract study of rheumatoid arthritis and hematopoietic cancers is underway. More complete mortality information on the rheumatoid arthritis cohort is being obtained by matching against the Social Security Administration and the VA Beneficiary Identification and Records Locator System mortality tapes.

Major Findings:

Investigations of Female Tumors

Analyses of information from the BCDDP study showed that age at menarche was significantly inversely related to breast cancer risk. A bilateral oophorectomy was associated with a lowered risk relative to natural menopause at a comparable age, which may reflect the more precipitous decline in endogenous hormones associated with surgery. Oral contraceptive use generally appeared unrelated to risk, except among women with multiple prior breast biopsies, who were at a twofold excess risk. The risk of breast cancer among women with P2 or DY parenchymal patterns as compared with N1 patterns was 2.7, an association comparable in strength but independent of other risk factors in this population.

In the case-control study of ovarian cancer in the Washington, D.C. area, menopause induced by hysterectomy, with preservation of both ovaries, was related to decreased risk. Infertility was associated with increased risk, apart from the effect of nulliparity. Parity was confirmed to be the most important protective factor, except in the serous subtype, suggesting that the histologic types should be considered separately. Tumors of low malignant potential shared the epidemiologic risk factor profile of invasive cancers.

The case-control study of epithelial ovarian cancer in Shanghai, China showed that, similar to high-risk areas, nulliparity increased risk (OR, OR=1.6) and number of births was inversely associated. Early menarche and late menopause were associated with increased risks, as was a history of ovarian cysts. Although oral contraceptive use was associated with decreased risk, there was some reduction in risk for those with a prior tubosterilization or IUD use.

Analysis of data from the case-control study of in situ cervical cancer in Australia found that women with more than seven sexual partners had a sevenfold increased risk compared to those with 0-1 partner. Risk also increased with duration of oral contraceptive use (OR=2.0 for more than 6 years of use), and with amount and duration smoked. Exposures to herpes simplex virus type 2 and cytomegalovirus as measured by antibody prevalence were unrelated to risk.

Results from the Latin American cervical cancer study indicated strong and independent effects on risk of multiple sexual partners and early ages at first intercourse. Detection of HPV types 16 and 18 (as measured by DNA filter in situ hybridization) was associated with a fivefold excess risk, although the measure was not correlated with sexual behavior. Surprisingly, an effect of multiple births persisted after adjustment for sexual and other variables, with risks rising to nearly fourfold for those with ten or more births. Smoking was a risk factor only among the subgroup of women who were HPV positive, and oral contraceptives were related to increased risk only for adenocarcinomas of the cervix. A relationship to cervical cancer risk of sexual behavior of the husbands was also apparent, although to a lesser extent than previously hypothesized.

Results from the study of cervical dysplasia, smoking, and papillomavirus infection suggested that smoking is a risk factor for dysplasia, independent of HPV infection. Infected nonsmokers had a relative risk of about four, while noninfected smokers had a risk of about two.

The interlaboratory study of HPV detection by southern blot revealed considerable variation in typing when this "gold standard" assay was used, enough to explain some of the discrepant findings in previously published research.

Analysis of data from the case-control study of complete hydatidiform mole showed that a prior full-term birth was associated with reduced risk, while previous abortions increased risk. A history of infertility was associated with reduced risk, but those who reported use of herbal medicine during a previous pregnancy were at excess risk. In addition, a statistically significant trend in risk was observed with years of oral contraceptive use.

In the case-cohort study of breast and endometrial cancers conducted within the prospective study in Sweden, positive trends with increasing total duration of estrogen treatment were found for both cancers. A protective effect of addition of cyclic progestins to treatment was not found for breast cancer, whereas for endometrial cancer no significant risk was found for estrogen usage that had been opposed by progestins. An additional case-control analysis evaluated the effects of several risk factors for breast and endometrial cancer in the cohort of women compared to the background population.

In the infertility follow-up study, most cancers occurred at expected frequencies, with the exception of cancers of the thyroid and other endocrine glands. Patients with progesterone deficiencies had a 20% overall higher risk than those with other causes of infertility, with excesses deriving primarily from cancers of the lung, cervix, endometrium, ovary, thyroid, and for melanoma. Breast cancer risk, however, was not elevated in all patients or

those with progesterone deficiencies, failing to support previous suggestions that this is a high-risk group.

Analyses within the prepaid health plans showed that the age-adjusted rate of breast cancer has risen from 69.2 in the early 1960s to 100.3 per 100,000 in the early 1980s. Adjusted for age and stage, the rates for estrogen receptor-positive tumors have more than doubled, while the rates for estrogen-negative tumors have risen only slightly, with the bulk of these increases presumably not due to any increase in use of mammographic screening. In the breast cancer case-control analysis, diazepam use was found to be associated with a risk of 0.7. There was, however, no consistent evidence of a dose or duration-response relationship. The analysis of data from the ovarian cancer study found that ovarian cyst was a major predictor of risk for early onset disease (<50 years), while uterine bleeding or progestin use were important risk factors for older subjects.

Other Investigations

The National Bladder Cancer Study 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. Risks of transitional cell carcinoma of the bladder in the United States among whites are approximately twice those among blacks. Although some of the differences in risk was due to confounding by cigarette smoking and occupation, whites remained at 60% increased risk compared to blacks after adjustment. The remaining difference in risk may be due, in part, to diagnostic differences.

Preliminary analysis of data from the leukemia and non-Hodgkin's lymphoma (NHL) study in Iowa and Minnesota suggested a relationship with use of some chlorinated hydrocarbon pesticides at least 20 years prior to diagnosis. There was no association of all leukemia or NHL with farming occupation. Suggestive associations were observed for both diseases with hair dye use, although the numbers of users were small.

The case-control study of childhood leukemia in Shanghai confirmed previous observations of an association of risk with intrauterine x-ray exposure. In addition, a significant dose-response relation was seen with use of certain antibiotics, including chloramphenicol. Other risk factors suggested were heavy birth weight, late birth order, and maternal exposure to chemicals during pregnancy.

Preliminary findings of the analysis of the case-control study of NPC in the Philippines indicate an increased risk associated with use of mosquito coils, and use of herbal medications. Tobacco smoking does not appear to be associated with increased risk, nor is Chinese ancestry. The expected elevation in EBV-antibody titers was observed in NPC cases. Interestingly, cases who reported use of herbal medicines demonstrated higher EBV-antibody titers than cases who did not.

In the first analysis completed using Veterans Administration hospitalization records, the expanded cohort of 5,161 white males with pernicious anemia was found to have significant excesses for all cancers (SIR=1.2) and cancers of the buccal cavity and pharynx (SIR=1.8), stomach (SIR=3.2), and for melanoma (SIR=2.1), multiple myeloma (2.1), myeloid leukemia (SIR=3.7) and other or unspecified leukemia (SIR=4.0).

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CONTRACT IN SUPPORT OF THIS PROJECT

WESTAT, INC. (NO1-CP6-1078)

Title: Continuation of Follow-up on Participants in the Breast Cancer Detection Demonstration Project

Current Annual Level: $320,677

Person Years: 1.5

Objectives: The main objectives of this project are to evaluate through a prospective study design such risk factors for breast cancer incidence as exogenous menopausal estrogen use, smoking, alcohol consumption, and diet; to determine etiologic factors for other cancers, such as lung, endometrial, ovarian and colorectal cancers; and to examine the effects of exogenous estrogens on mortality from heart disease, and hospitalization for fractures, gallbladder disease and diabetes.

Methods: This contract is funding a continuation of a cohort study initiated in 1981 on a sample of approximately 61,000 women who had previously participated in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening program co-sponsored by the National Cancer Institute and the American Cancer Society. Self-administered mail interviews are being collected biannually, yielding two interviews per subject during the five years of the study. Death certificates are being collected for all deceased subjects, and all newly diagnosed cancers are being validated through collection of operative and pathology reports.

Major Contributions: To date, 24 waves of questionnaires have been mailed to over 58,000 participants. The earliest waves of questionnaires have yielded response rates of approximately 90%. Nearly 600 subjects are known to be deceased, and death certificates have been requested. Validation procedures are underway to obtain verification of all reported cancers, and the first mailouts resulted in approximately 95% return rates from doctors or hospitals. All information is being keypunched, and computer files generated to allow analyses of these prospectively collected data.

ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

This is the sixth 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. In April 1989, Dr. Lois Travis was appointed an Expert with the Branch. During the past two years, she was a Supervisory Medical Officer with the Food and Drug Administration. Dr. Travis is Board-Certified in Clinical Pathology and Board-Eligible in Preventive Medicine. She completed her residency at the Mayo Clinic. In June 1989, Dr. Peter Inskip was appointed as a fellow under the Cancer Epidemiology and Biostatistics Training Program. He recently received his doctoral degree in epidemiology at the Harvard School of Public Health. Guest researchers during this past year included Dr. Jorgen Olsen from the Danish Cancer Registry, Copenhagen, Denmark; Dr. Wang Jixian from the Institute of Radiation Medicine, Tianjin, China; and Ms. Ylva Rodvall from the Institute of Environmental Medicine, Stockholm, Sweden. 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 England, Germany, Japan, Sweden, Denmark, Israel, Yugoslavia and the People's Republic of China. One staff member, Dr. Dale Preston, Expert Biostatistician, returned in June 1989 to the Radiation Effects Research Foundation as Chief of the Department of Statistics. The Branch was site visited in November 1988.

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. Better data are needed on which to base regulatory and other decisions about the potential hazard from medical, occupational, and environmental exposures, and to assess the value of exposure avoidance as a means of cancer prevention.

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, was completed. New cancers linked to radiation included cancers of the rectum and vagina. Very high doses, on the order of several hundred gray, were also found to increase the risk of cancers of the bladder and possibly uterine corpus, bone, cecum, and non-Hodgkin's lymphoma. For all female genital cancers taken together, a sharp dose response was observed. Doses on the order of several gray increased the risk of stomach cancer, and possibly kidney cancer, but not pancreatic cancer. Doses greater than 6 Gy to the ovaries resulted in a 23% reduction in breast cancer risk. A biochemical study of some 300 women with cervical cancer suggested that adrenal damage by radiation may have lowered estrogen and androgen levels and contributed to a low breast cancer risk, which was evident even among postmenopausal women. Despite an average dose of 0.31 Gy, no overall risk was found for direct exposure to the breast; however, there was a suggestion of a dose response among women whose ovaries had been surgically removed. Radiation was not found to increase the risk of cancers of the small intestine, colon, and vulva, and Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia. A twofold risk of radiogenic thyroid cancer was suggested following an average dose of 0.11 Gy.

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. A study of 3,000 children treated for lymphoid hyperplasia with radiation or surgery in Boston was completed. 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. An excess of both thyroid cancer and nodules in the exposed population was identified following a mean dose of 0.24 Gy. However, risk estimates derived from a mail survey were much higher than those from a clinical examination, suggesting that questionnaire studies of thyroid cancer might be misleading due to underascertainment of thyroid diseases in the nonexposed populations. 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 0.09 Gy. For the first time a dose-response relationship for radiogenic tumors of the central nervous system was found. Elevated risks of skin cancer and leukemia were also linked to scalp radiotherapy. A biochemical epidemiologic study has continued to evaluate whether the risk of radiogenic thyroid cancer (and skin cancer) might be related to increased host susceptibility associated with heterozygosity for ataxia-telangiectasia. Ataxia-telangiectasia is a genetic disorder relatively common among North Africans; and 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. 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, thyroid cancer was associated with high-dose radiation therapy as evidenced by a strong dose-response relationship. Exposures as high as 60 Gy 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 cancers of the thyroid.

The risk of cancer following multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 was further evaluated in Massachusetts, Connecticut, and Canada. The study of over 13,385 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. A modest increased risk of cancer of the esophagus was suggested. In contrast, no excess risk of lung cancer was found, despite average cumulative doses of 0.84 Gy, and no consistent dose response was seen for leukemia or multiple myeloma. A similar study of tuberculosis patients in Connecticut found a high risk of breast cancer among women receiving multiple chest fluoroscopies prior to age 30 years. Cancers were identified by linking patient rosters with records in the Connecticut Tumor Registry. Collaborative mortality analyses of tuberculosis patients in Canada also confirmed the linearity of the dose response for radiogenic breast cancer and the decreasing sensitivity with age at exposure.

A study was conducted of 1,030 women with scoliosis seen at four Minneapolis-area hospitals between 1935 and 1965. These women received large numbers of spinal x-ray examinations during adolescence to monitor spinal curvature. The risk of breast cancer was found to increase with increasing number of x-rays and with increasing radiation dose to the breast (mean = 0.12 Gy). These data suggest that frequent exposure to low-level diagnostic radiation during childhood or adolescence may increase the risk of breast cancer.

To evaluate whether diagnostic x-rays increase the risk of adult leukemia and lymphoma, a case-control study was conducted within two Kaiser prepaid health plans. Patients with leukemia (n=632), non-Hodgkin's lymphoma (NHL; n=324), and multiple myeloma (n=243) were matched to controls (n=1,431). Over 30,000 x-ray procedures were abstracted from hospital records and categorized, eliminating the possibility of response bias associated with interview studies. No association was found for chronic lymphocytic leukemia (RR=0.9; n=247), one of the few malignancies never linked to radiation. For all other forms of leukemia combined (n=385) there was a significant increase in risk with increasing number of x-rays; however, this trend progressively diminished when x-rays near the time of diagnosis were excluded. Patients with NHL were x-rayed more often than controls (RR=1.60); but the RR fell to 1.1 when x-rays within 2 years of diagnosis were ignored. These data suggest that x-rays might not be causal factors but simply related to conditions that portend the development of leukemia or NHL. For multiple myeloma, there were suggestive increases in risk that were not diminished by excluding x-rays in the intervals before diagnosis.

Case-control studies of long-term survivors of breast cancer are being conducted in Connecticut and Denmark to learn whether the increased risk of second breast cancer might be related to radiation therapy, especially among women treated after age 40. No risk of leukemia was linked to radiotherapy for breast cancer, providing further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue. Women irradiated for Hodgkin's disease at a young age were found to be at high risk for developing breast cancer.

The incidence of thyroid cancer was evaluated in 35,074 patients examined for suspected thyroid disorders between 1951-1969 in Sweden with an average of 1.92 MBq of iodine-131 (0.5 Gy to thyroid). Record-linkage with the Swedish Cancer Registry identified 50 thyroid cancers occurring 5 or more years after initial iodine-131 examination, in contrast to 39.4 expected (RR=1.27). Patients anticipated to be at highest risk, i.e., women (RR=1.1) and those observed for 10 or more years (RR=0.9), showed no evidence of a dose response. Overall, these data provide little proof that iodine-131 is carcinogenic in man and support the notion that the carcinogenic potential of internal iodine-131 beta particles might be at least four times lower than that of external x-rays or gamma rays. Further, an analysis of all incident cancers following exposure to diagnostic doses of iodine-131, found no overall excess cancer risk, although a slight increase in leukemia is being evaluated further.

The time course and dose dependence of the incidence of bone sarcomas among 900 German patients treated with high doses of radium-224 have been analyzed in more detail. The distribution of excess bone sarcomas over time appears very similar to that seen for leukemia among the atomic bomb survivors, i.e., risk appears within 2 to 4 years after exposure and decreases to near normal levels after about 25 years. For a total dose of radium-224, the effectiveness of inducing bone sarcomas appears to increase when the exposure is spread over time. For the first time, an excess of breast cancer and liver cancer has appeared. There was no increase in leukemia.

Epileptic patients given radioactive Thorotrast during cerebral angiography in Denmark were found to be at very high risk for subsequent development of liver cancer and leukemia. An increase in lung cancer was also noted that might be due to continuous exhalation of the thoron gas that is a byproduct from the decay of Thorotrast.

A twofold risk of leukemia was observed among 4483 women irradiated for benign bleeding disorders, between 1925 and 1965, in Massachusetts and Rhode Island, following average bone marrow doses of 0.53 Gy. This treatment appeared to result in a greater risk per gray for leukemia compared with higher doses used to treat cervical cancer, which may be due to the decreased likelihood of sterilizing potentially leukemic cells. These data will be combined with similar data on 8,000 women from New York and Connecticut for further evaluation of dose-response relationships for leukemia and other cancers.

A variety of analytic studies are underway. A population-based case-control study is being conducted among women treated for cancer of the uterine corpus to evaluate the dose-response relationship between radiation dose and risk of leukemia. A study of the carcinogenic effects of radiation therapy for peptic 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 18,000 persons who received therapeutic doses of radioactive iodine in Sweden. A feasibility study in Israel showed that it will be possible to evaluate 30,000 persons given diagnostic iodine-131 for subsequent risk of thyroid cancer. This study has been expanded to include Yugoslavia. Studies of over 2,000 women treated for infertility in New York and Israel have continued. A feasibility study of children receiving multiple chest fluoroscopies during heart catheterization was successfully completed at hospitals in the United States, England, and Israel; investigations in the Netherlands continue. An approach for studying patients receiving neutron therapy for cancer was developed and feasibility studies were initiated. A large-scale collaborative study with the Children's Cancer Study Group was initiated to learn more about the causes of childhood leukemia. The possible role of low frequency electromagnetic field radiation will be evaluated. 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, Food and Drug Administration, 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 humans. 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. 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 Hiroshima and Nagasaki 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 since 1979 by a multi-year research contract with the U.S. National Academy of Sciences.

Current information on breast cancer risk among A-bomb survivors indicates that women exposed as children or teenagers were at greatest risk and that women over 40 at the time of the bombings were at least risk. The excess did not appear until the ages in later life when breast cancer risk normally becomes appreciable. Subsequently, the excess remained constant over time relative to the age-specific baseline risk for breast cancer. A case-control interview study was conducted to investigate the possible interactions of breast cancer risk factors with radiation in the causation of breast cancer. Early age at first full-term pregnancy was found to protect against radiation-induced breast cancer among exposed women. The high risk of radiation-related cancer among women exposed at young ages may arise because such exposures tended to occur before the first pregnancy.

Apparent differences between A-bomb survivors and U.S. uranium miners with respect to radiation-induced lung cancer risk, especially as related to age, time after exposure and smoking history, prompted a binational pathology review of tissue samples from the two series. Preliminary results suggest that there are consistent differences by cell type, smoking history, and radiation dose.

Hormonal and micronutrient assays of stored serum samples for cancer cases diagnosed subsequent to blood drawing and matched controls have been carried out at RERF and at collaborating laboratories in Japan. Thus far the only positive association that has emerged is evidence of lower iron levels among persons who later developed stomach cancer. Other studies in progress include case-control studies of colorectal and thyroid cancers, and a cohort-based survey of colorectal cancer incidence.

A major initiative, taken in collaboration with the RERF Histopathology Laboratory, tumor and tissue registries, and the Department of Epidemiology, is to enlist the cooperation of local pathologists to conduct a new series of site-specific cancer incidence studies. The new studies will rely on local sources of information and also will actively seek out information from national and regional registries from areas other than Hiroshima and Nagasaki. Address histories will be obtained for cohort members from a variety of sources, of which the main ones are RERF records and files maintained by national and local government agencies. The first such study of breast cancer incidence during 1950-1985 has been initiated.

The effect of the new dosimetry changes on risk estimates has been evaluated. In terms of total kerma (essentially whole-body gamma ray plus neutron exposure), the risk estimates are 75% to 85% higher with the new dosimetry. At an assumed constant relative biological effectiveness of 10 for neutrons, the effect of the dosimetry revisions is to increase organ dose risk estimates, relative to those based on the old dosimetry, by 40% for nonleukemia and 80% for leukemia. The linearity of the dose-response relationships has been questioned in that a leveling off at high doses is seen for several sites.

Occupational and Environmental Exposure Studies: Although the possibility of increased cancer risk associated with chronic occupational exposure to x-ray and gamma ray 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. Two of the most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, are being evaluated. Preliminary results from some 80,000 responses to a mail questionnaire suggest a twofold risk of thyroid cancer, although this excess may be related to personal x-ray exposures rather than occupational exposures.

Cancer incidence among 27,011 diagnostic x-ray workers was compared to that of 25,782 other medical specialists employed between 1950-1980 in China. X-ray

workers had a 50% higher risk of developing cancer than other specialists not frequently exposed to radiation during employment. Cancers linked to radiation work included leukemia, breast and thyroid, and possibly bone and skin. High risks of cancers of the esophagus and liver were not consistent with a radiation effect and might reflect differences between groups of hospital workers in social class, alcohol intake, dietary habits, and other risk factors. The excess leukemia followed a wave-like pattern, peaking 10-14 years after start of employment and decreasing to normal levels after 20 years. No excess lung cancer or multiple myeloma were observed.

Studies to evaluate cancer mortality among radiation workers are ongoing. Preliminary results from one investigation suggest that the dosimetry records from a large commercial company will be useful in evaluating the long-term health effects of chronic occupational exposure to radiation. Cumulative doses as high as several gray among workers were identified, and record-linkage with the National Death Index was able to identify deaths occurring since 1979. A study of workers at one nuclear power plant developed a feasible, although labor intensive, approach to obtain cumulative radiation doses for both utility and contract employees. However, the results demonstrated the need for the Nuclear Regulatory Commission to consider a modification of their reporting requirements to include annual doses with personal identifiers. If changed, a registry of radiation workers could be effectively created. It is anticipated that these proposed modifications will be in place by 1991.

Approximately 2,000 women in China were evaluated for nodular thyroid disease by physical examination. Women residing in areas of high natural background radiation due to radioactive monazite sands were not found to have a higher prevalence of thyroid nodules or cancer than women residing in other areas of southern China. The cumulative dose to the thyroid was estimated to be between 0.08 and 0.18 Gy, and the absence of any differences suggests that protracted exposures to very low levels of ionizing radiation throughout life are not associated with a detectable increase in thyroid nodular disease.

Radon exposure in the home has been suggested as an important risk factor for lung cancer, and collaborative case-control studies are ongoing in New Jersey, Missouri, Sweden and China. Comparisons of measurements made in Swedish dwellings showed a good correlation between thermoluminescence dosimeters placed in dwellings for two weeks, and alpha track detectors placed in dwellings for six months and for one year. However, seasonal variations were such that for the purpose of risk assessment in epidemiologic studies, measurements for a whole year may be preferable to those for shorter intervals.

Acquisition of data for the study of cancer mortality in the vicinity of nuclear facilities was completed. This study was initiated in light of reports suggesting an increased risk of childhood leukemia associated with living near such facilities in Great Britain. All electric power reactors that ever were operational and that exceeded nominal power output have been included in addition to military reactors and fuel reprocessing plants. Mortality in counties with or near these plants is being compared with mortality in counties with similar demographic and socioeconomic characteristics.

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 NCI's Environmental Epidemiology Branch and the Division of Cancer Treatment, a systematic study of therapeutic drugs continues. Occasionally, it has been possible to evaluate other drug exposures in populations that have been studied primarily for other reasons.

A study of women treated with melphalan or chlorambucil for ovarian cancer in five randomized clinical trials previously found a very high risk of leukemia. This study was expanded to include patients treated at the Mayo Clinic and at the M. D. Anderson Hospital. Comparative analyses indicated that the leukemic potential of cyclophosphamide is significantly lower than that of melphalan. These data are to be combined with data from breast cancer clinical trials to evaluate more clearly the patterns of leukemia risk by time, age, dose and other factors. Studies of low-dose adjuvant chemotherapy did not find an increase of leukemia following exposure to antimetabolites such as 5-fluorouracil (5-FU). Ongoing studies include the evaluation of patients with colorectal cancer and lung cancer who have received nitrogen mustard, cytoxan, methotrexate, and lomustine in the Veterans Administration clinical trials system; and an evaluation of patients treated with triethylenethiophosphamide and 5-FU in early clinical trials of breast cancer.

A case-control study of 220 children with second malignant neoplasms and 400 controls is currently being analyzed 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. Alkylating agents were not found to be associated with an increase of subsequent thyroid cancer.

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 two 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, Iowa, Detroit, Los Angeles, and Atlanta to clarify the possible association of leukemia and preleukemia among breast cancer patients treated with adjuvant chemotherapy. The leukemia risk for the two most frequently used alkylating agents, melphalan and cyclophosphamide, will be quantified and compared, and the dose-response relationship will be estimated. Results from a feasibility study in Connecticut indicate an 11-fold increased risk of acute leukemia and preleukemia after alkylating agent therapy and suggest a higher risk for melphalan than for cyclophosphamide.

The SEER registries are being used to examine the risk of second tumor development associated with various treatments for the primary cancer. In particular, solid tumors appearing five or more years after initial treatment with alkylating agents for 17 primary cancers are being evaluated for possible detailed field investigation. Chemotherapy for non-Hodgkin's lymphoma was found to increase the risk of bladder cancer among long-term survivors, presumably an effect of cyclophosphamide.

Epileptic patients were not found to be at elevated risk for cancer development, despite prolonged exposure to phenobarbital and other anti-convulsive drugs. A study continues 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, endometrium, and cervix, and non-Hodgkin's lymphoma and Hodgkin's disease. Patients with cutaneous T-cell lymphoma were found to be at significant risk of developing a second cancer (RR=1.7). Excesses of lung cancer may have been due to an altered immune status; increased colon cancers may provide clues to common exposures or susceptibility mechanisms.

Laboratory Studies: A number of cytogenetic studies have been added to epidemiologic investigations to determine the usefulness of somatic cell chromosome aberrations in circulating lymphocytes as biological dosimeters following partial body radiation exposure. Cytogenetic aberration data are being evaluated in six 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, tuberculosis patients who received multiple chest fluoroscopies, women irradiated for benign gynecologic disorders, and cancer patients treated with neutrons. 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, thyroid stimulating hormone and antimitochondrial antibody. 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 two 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 continuing among atomic bomb survivors of the relationship between cancer induction and levels of hormones and micronutrients in sera obtained prior to cancer diagnosis.

Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased aberrations were detected up to 35 years after exposure, indicating that radiation damage can persist for extremely long periods of time. Overall, the percent of aberrant chromosomes was much lower than expected based on data from the atomic bomb survivor study. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients given localized high-dose radiotherapy is the result of cell-killing effects of radiation. Significant elevations for unstable chromosome aberrations were also found for populations treated for enlarged thymic glands and tonsils, and who received multiple chest fluoroscopies during pneumothorax therapy for tuberculosis.

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 is being applied to breast cancer incidence data and 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. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of baseline 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. Development of a package of epidemiologic programs for personal computers is nearing completion. Several of these programs were used by the National Academy of Sciences BEIR IV committee in their analyses of the risks associated with radon exposure, and they are currently being used by the BEIR V committee as the primary tool for the analysis of data from a wide variety of studies of radiation effects.

The risk of radon-induced lung cancer among residents of single family homes in the U.S. was estimated using models recently developed by the National Academy of Sciences BEIR IV Committee. These models predict that approximately 9% of all lung cancer deaths (about 13,300 deaths per year) may be due to indoor radon exposure. The attributable risk is highest among men and among smokers. Most of the contribution to the attributable risk arises from exposure rates below 4 pCi/l for which no remedial action is recommended.

Workshops: Two workshops were held this year concerning the carcinogenicity of internal emitting radionuclides. All the major studies of radium and Thorotrast exposure were represented at an international workshop whose proceedings will be published as a supplement to the British Journal of Radiology. A small meeting

was held on radioactive iodine where representatives from Sweden, Yugoslavia and Israel presented approaches to studying the effects of low-dose diagnostic iodine-131.

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 survey of cancers following medical irradiation, an evaluation of the statistical and epidemiologic issues concerning estimation of cancer risk from low doses of ionizing radiation, a review of the possible risks of radiotherapy for breast conservation treatment, and overviews on the importance of latent period, risk projection and time-response models in estimating cancer risks. 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 National Aeronautics and Space Administration, the International Commission on Radiation Protection, and the World Health Organization, among others. At times staff members have become heavily involved in controversial public policy issues and debates, most recently with the issue of possible cancer risk associated with living near nuclear installations in the United States.

In collaboration with NCI's Biostatistics, Clinical Epidemiology 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 (SSA), Internal Revenue Service (IRS), National Center for Health Statistics, Health Care Finance Administration, U.S. Postal Service, Veterans Administration, and various state departments of vital statistics). Efforts continue to be made to assist the Nuclear Regulatory Commission in establishing a registry of radiation workers that could be used to investigate the effects of exposure to ionizing radiation. Initiatives to develop and coordinate national data resources continue to be made that, with appropriate safeguards, may be tapped by qualified investigators throughout the country. Efforts continue to extend, retroactively, coverage of mortality before 1979 when the National Death Index began. An extension for 1977 and 1978 has been initiated. Progress was made in obtaining from the SSA essential information for follow-up studies, and IRS agreed to change its agreement with the National Institute for Occupational Safety and Health under which IRS addresses are provided for occupational studies--the changes 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, and mortality follow-up of veterans who completed questionnaires in the 1950s on smoking and occupation continues.

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, Germany, Sweden, Israel, and the People's Republic of China.

New directions and ongoing research projects of the Radiation Epidemiology Branch undergo critical review. Oversight and evaluation are 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 Study of Cancer Among Populations Residing Near Nuclear Facilities); 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 (24 contracts) 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 population 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 (43 versus 10.7 expected) and benign tumors of the thyroid (55 versus 27.3), tumors of the nervous system (60 versus 8.7), and leukemia (13 versus 4.7) are associated with scalp irradiation during childhood. A paper on the mortality experience of these children has been published in the American Journal of Epidemiology, one paper on radiation-associated neural tumors has been published in the New England Journal of Medicine and one on radiation-induced thyroid tumors was submitted for publication. A manuscript on the association between scalp irradiation and skin tumors is in preparation. 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 extension of a biochemical epidemiologic study 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 cancer in this population will be conducted.

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 contra-lateral breast, and, if such a risk exists, to evaluate the dependence of risk on dose and age at exposure. Study subjects have been drawn from approximately 50,000 women with breast cancer reported to the population-based tumor registry

in Denmark between 1943-1975. Cases are all women with breast cancer who developed a second primary breast cancer ten or more years after treatment for the first malignancy. Controls are women with a primary breast cancer who did not develop another breast cancer. One control has been 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. Individual dosimetry determinations are being made. Record abstraction is continuing.

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 have been used to identify the study cohorts. For those patients treated by x-rays, estimates of radiation doses to specific organs are being determined. Death certificates have been obtained for those who have died and the vital status, as of 1984, has been ascertained. Analyses are in progress, and malignancies of particular interest include the stomach, pancreas, colon and lung, and leukemia.

Second Follow-up Study of Patients Treated for Hyperthyroidism. Ionizing radiation is widely known to be carcinogenic; however, the risks of exposure to radioactive iodine (I-131) are not well defined. The evaluation of potential risks associated with I-131 exposure is important since it is widely used in both medical diagnosis and therapy, is one of the primary release products in nuclear power generation, and is a major component of fallout from nuclear weapons testing. Since 1984, the National Cancer Institute has been involved in conducting a second follow-up of hyperthyroidism patients who were enrolled in the U.S. Thyrotoxicosis Therapy Follow-up Study, and were still living in 1968 to evaluate further mortality in relation to I-131 exposure. In 1961, the Cooperative Thyrotoxicosis Therapy Follow-up Study patients were treated for hyperthyroidism between 1946-64 at 18 medical centers in the United States and one center in the United Kingdom. Many tracing resources have been utilized to ascertain current vital status, including credit bureaus, departments of motor vehicles, state mortality files, the Social Security Administration mortality tapes, records from the Health Care Financing Administration, the National Death Index, telephone and other directories, voter registration listings, and other sources. For individuals determined to be deceased, death certificates are being requested to determine the causes of death.

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. Over 40,000 patients exposed to diagnostic 131-I between 1950-1970 have been identified in seven hospital centers in Sweden. Approximately 20,000 patients treated by 131-I for hyperthyroidism and 6,000 patients treated by 131-I for thyroid cancer between 1951-1975 have been identified at these same seven centers. Medical and therapy information are being abstracted from the patient hospital record. Follow-up is being 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 7 years of study (1951-1957) are being 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. Two manuscripts on the population of patients receiving diagnostic 131-I have been published. There was no evidence of an increased risk of thyroid cancer or any other cancer among 10-year survivors.

Recently, two more centers have been added to this investigation. Approximately 25,000 patients exposed to diagnostic 131-I between 1963-1979 have been identified in one medical center in Slovenia, Yugoslavia and 34,000 patients examined between 1955-1979 were identified in Israel. Medical and treatment data are being abstracted from hospital records. Cancers will be ascertained by record linkage with population-based cancer and death registries. As in the Swedish cohort, expected number of cancers will be computed based on age-, sex-, site-, and calendar-time-specific incidence data from the cancer registries. Data abstract forms were prepared and data collection is currently underway. A meeting of the Swedish, Yugoslavian, Israeli, and U.S. collaborators was held to discuss study methods and future analyses.

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 145,000 radiologic technologists certified by the American Registry of Radiologic Technologists since its inception in 1926. Optical scan questionnaires were sent to all 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. Questionnaires have been completed on over 103,000 technologists. Death certificates are being procured for about 6,000 deceased subjects. Cancers reported on questionnaires or death certificates are being histologically confirmed. Preliminary findings suggest higher than expected incidence of thyroid and endometrial cancers. Quantitative estimates of radiation exposure are being made for all questionnaire respondents based on length of employment, types of procedures performed, and personal diagnostic and therapeutic x-ray exposures. Record linkage with dosimetry files of a national company are also being made. Excess cancer incidence and mortality will be evaluated in relation to radiation exposure. Additionally, nested case-control studies have been 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, are being ascertained from employers and from the nation's largest dosimetry company. One manuscript has been published, and another has been drafted for publication which describes the methodology and descriptive population characteristics. It is anticipated that all data collection activities will be completed this year. In-depth analyses of the data will begin shortly thereafter.

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.

Incidence data for 1950-80 for cancers of the female breast, colon, and rectum are being reanalyzed in terms of the DS86 dosimetry, which is still being calculated for groups of survivors with non-standard shielding configurations. This work will culminate in a new manuscript on breast cancer and a revised manuscript on colorectal cancer. A manuscript on the methodology of a nested case-control study of breast cancer, with matching on radiation dose, has been prepared and submitted for publication. Analyses of main effects for factors other than radiation dose, and of interactions of these factors with radiation dose, have been completed and two separate manuscripts are in preparation. Data are being analyzed for a case-control interview study of colorectal cancer, and data collection has been completed and a data set has been received for a case-control study of thyroid cancer. Stored serum samples from cancer cases and controls, obtained in 1971-73, 5 or more years before cancer diagnosis, have been assayed for hormonal and micronutrient content and analysis is proceeding. The first manuscript, on ferritin and transferrin levels in relation to subsequent lung cancer and stomach cancer risk, has been completed and submitted for publication. Additional information on menopausal status has been obtained by interview to assist in analyses of hormonal levels among breast, endometrial, and thyroid cancer cases and controls at the time of blood drawing in 1972-73. Data from an international pathology review of diagnostic material for high-dose and low-dose lung cancer cases from the A-bomb survivors and from U.S. uranium miners are being analyzed to see if there are consistent patterns with respect to population, radiation dose, smoking history, and type of radiation exposure. A draft manuscript has been prepared on esophageal dysplasia, alcohol consumption, and radiation dose among autopsy cases without clinical evidence of esophageal cancer. A platform protocol, prepared by collaborating investigators in the Branch and at RERF, for studies of cancer incidence in the LSS sample has been formally adopted by RERF. This protocol is intended to help with the enlistment of collaborators, particularly in pathology, from the Hiroshima and Nagasaki medical communities, to improve the tissue and tumor registries, and to provide a standard approach for ascertainment from local and non-local sources. Non-local sources are particularly important for sites with low early fatality rates, like the thyroid gland and female breast, because of extensive migration to other parts of Japan by younger cohort members. An address data base is to be constructed by consolidating all the address information available at RERF in computerized form or as written documents, and by collecting information from outside

sources such as the Atomic Bomb Survivors Handbook, data maintained at Hiroshima, Nagasaki, and other government offices. A mail survey and attachments from family registry records will be used to fill in information not attainable by cheaper means. The first study to be conducted under the protocol is a new breast cancer incidence survey, for which case ascertainment began this year.

The following findings were obtained: Increased power for main effects, and greatly increased power for interactions of main effects with dose, are obtained with matching on dose for a nested case-control study, provided that good dose-response information is available from a prior study of the underlying cohort. In the breast cancer case-control study, the usual breast cancer risk factors were operating, and in particular those related to a protective effect of early age at first full-term pregnancy. In this population, for which extended breast feeding is traditional, a strong protective effect of lactation is apparent which is not entirely explained by early age at first delivery. Ovariectomy and surgical menopause were protective, but no evidence was found for higher risk associated with early menarche or late natural menopause. Interaction analyses tend to indicate synergistic relationships between certain risk factors and radiation dose. For women exposed to similar radiation doses at similar ages, the likelihood of subsequent breast cancer was more than twice as high if no pregnancy had occurred by the time of exposure than for parous women. Regardless of reproductive status at the time of exposure, radiation-induced breast cancer was less likely among women who experienced their first deliveries at young ages, who had many children, or who had lengthy lactation histories. In the colon cancer incidence study, risk is strongly related to radiation dose, especially for cancer of the sigmoid colon. Interview data confirm that high exercise levels are associated with reduced colon cancer. In the hormonal and nutrient-assay studies, it appears that low ferritin levels are associated with subsequent stomach cancer risk; this may possibly be linked to undetected internal bleeding. No relationship was observed for lung cancer. No significant differences were observed between breast cancer cases and controls with respect to prolactin, total estrogen, SHBG, non-SHBG-bound estrogen, or DHEA sulfate. Esophageal dysplasia in autopsy cases appears to be strongly related to alcohol consumption, but not to radiation dose despite evidence that esophageal cancer risk is dose-related. For breast tissue, on the other hand, it appears that dysplasia is related to radiation dose in a way that parallels the risk of breast cancer.

Prenatal X-ray Exposure and Childhood Cancer in Twins. The objective of this study 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 had 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 record 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.

About 100 cases of childhood cancer and 200 comparison subjects have been identified for study and their medical records and those of their mothers have been reviewed. This sample size is sufficient to detect a doubling of risk with a high probability. An analysis has been carried out which included the number and kind of x-ray exposures, stage of pregnancy at exposure, birth weight, duration of gestation, medical complications of pregnancy, and other variables that might confound the comparison. The relative risk with abdominal exposure was 1.4 for all cancer and 1.7 for leukemia. Although this excess risk was not statistically significant, its magnitude is consistent with previous findings. Overall childhood cancer incidence among twins is being compared with that of single-born subjects. The previously reported reduced cancer risk associated with twinning is also relevant to the main objectives of this investigation.

Diagnostic X-rays and Risk of Leukemia and Lymphoma. To evaluate whether diagnostic x-rays increase the risk of adult leukemia and lymphoma, a case-control study was conducted within two Kaiser prepaid health plans. The contracts with the Kaiser Research Foundation in Oakland [NO1-CP-41058] and Portland [NO1-CP-41059] are listed under the Environmental Studies Section, Environmental Epidemiology Branch, Division of Cancer Etiology. Patients with leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma were matched to controls on the basis of sex, age, calendar year, and length of membership. Over 30,000 x-ray procedures were abstracted from hospital records and categorized, eliminating the possibility of response bias associated with interview studies. Dose response was evaluated by assigning each x-ray procedure a score based on probable bone marrow dose. No association (ever/never) was found for chronic lymphocytic leukemia, one of the few malignancies never linked to radiation. For all other forms of leukemia combined there was a significant increase in risk with increasing number of x-rays; however, this trend progressively diminished when x-rays near the time of diagnosis were excluded. Patients with NHL were x-rayed more often than controls (RR=1.60); but the relative risk fell to 1.1 when x-rays within two years of diagnosis were not counted. These data suggest that x-rays might not be the causal factors but simply related to conditions that portend the development of leukemia or NHL. For multiple myeloma, there were suggestive increases in risk which were not diminished by excluding x-rays in the time intervals near diagnosis.

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 are being matched to vital statistics records and

the Israeli Cancer Registry. Linkage is 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 preleukemic conditions, and to quantify and compare the leukemia risk for the two most frequently used alkylating agents, melphalan and cyclophosphamide. Record linkage studies in five population-based cancer registries (Connecticut, Iowa, Detroit, Los Angeles, and Atlanta) have identified 108 cases of women with breast cancer who developed subsequent leukemic disorders. Three controls for each case have been selected from a pool of breast cancer patients who did not develop a second cancer. Complete treatment histories are being abstracted from hospital charts and physician records. If sufficient data are available, the dose-response relationship will be examined.

Cancer Risk in Epileptics and Their Offspring Following Anti-Convulsive Drug Exposure. A study has been completed 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 have been linked with hospital lists to ascertain cancers. Cancer risk was not elevated among long-term users of anti-convulsive drugs. The risk of cancer in the epileptics is being correlated with any past exposure to thorotrast which would accompany cerebral angiography. A preliminary cohort investigation has been conducted. Data analysis are ongoing.

Study of Thyroid Cancer and Nodularity in High Radiation Background Areas in China. Over 2,000 women were examined to learn whether cumulative lifetime exposure to high background radiation is associated with a detectable increase in thyroid disease in China. Analysis of examination findings and blood studies, including chromosomal data was completed, and a meeting of Chinese and U.S. collaborators took place at NIH to discuss study findings and prepare a report for publication.

Studies of Radiation Workers with Individual Dosimetry Determinations. Since 1985, the Radiation Epidemiology Branch, National Cancer Institute, has contracted with Tech/Ops Landauer, Inc., a company providing monthly radiation dosimetry determinations for more than half the radiation workers in the United States, to obtain dosimetry support for an ongoing study of over 145,000 x-ray technologists certified by the American Registry of Radiologic Technologists. Intense record searches have been performed for information dating as far back as 1953, and record linkages with computerized records dating back to 1978 have been performed. These searches have proven useful in characterizing the radiation exposures received by this large population during a high percentage of their working careers. Additionally, a pilot investigation was conducted to evaluate whether a dosimetry registry of radiation workers could be created, similar to what has been done in Canada and the United Kingdom. Tech/Ops Landauer clients are distributed nationally and represent nearly all radiation-exposed occupational categories, including workers in nuclear power plants, medical facilities, educational institutions, industry, and government. Since 1970, approximately one million individual records are available with the following information: last name, first name, middle initial, Social Security

Number, month, day, and year of birth, sex, annual radiation dose, cumulative "lifetime" dose, and neutron dose. The results of the pilot study suggested that at reasonably low cost a registry of over 700,000 workers registered with Tech/Ops Landauer, Inc. in 1978 and thereafter could be created, cumulative exposures accurately estimated in large part, and Social Security mortality files and National Death Index files accessed for death information.

Second Cancers Following Radiotherapy for Uterine Corpus Cancer. The objective of this study is to quantify the relationship between radiation dose and second cancer risk in a population of women treated for uterine corpus cancer. In the first phase of this study, there were 236 cases of leukemia following uterine corpus cancer and 771 matched controls with cancer of the uterine corpus were identified from 9 population-based cancer registries in the United States, Canada and Europe utilizing the record-linkage Master Agreement mechanism. Medical records are being abstracted and radiation dose records photocopied for each study subject. Leukemias are being reviewed and reclassified by the study hematologist. Radiation dose to the active bone marrow will be estimated for 14 segments of the bone marrow. Generalized relative risk functions will be fit to the data to describe the dose-response relationship, and the results will be compared to risk estimates obtained from the Cervical Cancer Study using the linear-exponential and quadratic-exponential risk models. Of particular interest in this study will be a comparison of the effect of dose fractionation from external beam therapy with the effect of continuous exposure from brachytherapy. In addition, the pattern of radiation-induced leukemia risk will be examined by time since initial treatment, and age and calendar year of exposure.

In the second phase of this study, a cohort study involving approximately 500,000 patients will be identified to evaluate the risk of second primary cancer following treatment for uterine corpus cancer by time since treatment and age at first treatment. The results of this study will be used to select additional organ sites which might be valuably pursued in a future detailed case-control or case-cohort investigation.

Etiology of Childhood Leukemia. The objectives of this study are to determine whether lifetime residential exposure to low frequency electromagnetic field (EMF) increases the risk for childhood leukemia. A subset of cases and controls enrolled in the U.S. Childhood Cancer Study Group (CCSG) will be evaluated for exposure to EMF. Measurements of EMF in current and former residences and schools of 1,000 cases and 1,000 controls will be carried out by a special measurement organization, to be selected through a separate solicitation and to be funded through a distinct contract. Current occupants of the residences to be evaluated will be identified and arrangements with school officials to gain access to the schools will be made so that measurements of EMF can be carried out.

RADIATION EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 89

Institution/Principal Investigator/ Contract Number	Title
Chaim-Sheba Medical Center 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
Connecticut Department of Health Services Maria J. Schymura NO1-CP-51041-01	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Danish Cancer Registry Hans H. Storm NO1-CP-51055-04	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Danish Cancer Registry Hans H. Storm NO1-CP-51037	Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer
Israel Cancer Registry Leah Katz NO1-CP-85635-01	Record-Linkage Study of Patients Exposed to Diagnostic Radioactive Iodine
Karolinska Institute Lars-Erik Holm NO1-CP-51034	Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure
Minnesota, University of Jack S. Mandel NO1-CP-21015	Risk of Cancer in X-Ray Technologists
National Academy of Sciences Charles Eddington 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

Ontario Cancer Treatment Foundation Eric J. Holowaty NO1-CP-51047-01	Leukemia Following Radiotherapy for Uterine Corpus Cancer
R.S. Landauer, Jr. & Company R. Craig Yoder NO1-CP-61083	A Feasibility Study of Radiation Workers with Individual Dosimetry Determinations
Slovenia Cancer Registry Vera Pompe Kirn NO1-CP-85634-01	Record-Linkage Study of Patients Exposed to Diagnostic Radioactive Iodine
Southern California, University of Leslie Bernstein NO1-CP-51035-02	Leukemia Following Radiotherapy for Uterine Corpus Cancer
State Health Registry of Iowa Peter Weyer NO1-CP-51042-01	Leukemia Following Radiotherapy for Uterine Corpus Cancer

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04481-13 REB

PERIOD COVERED: October 1, 1988 to September 30, 1989

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)

PI:	J.D. Boice, Jr.	Chief	REB	NCI
Others:	C.E. Land	Health Statistician	REB	NCI
	Z. Hrubec	Expert Statistician	REB	NCI
	R.A. Kleinerman	Epidemiologist	REB	NCI
	E. Ron	Senior Staff Fellow	REB	NCI
	S. Jablon	Expert Statistician	REB	NCI
	R.E. Curtis	Statistician	REB	NCI

COOPERATING UNITS (if any): Radiation Effects Research Foundation, Japan (S. Abrahamson); Michael Reese Hospital (A. Schneider); Department of Energy (R. Goldsmith); Karolinska Institute (L.-E. Holm); Harvard University (B. MacMahon)

LAB/BRANCH: Radiation Epidemiology Branch

SECTION:

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20892

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 risk in populations exposed to ionizing radiation; (2) characterizes risk by dose, radiation quality, fractionation, time, sex, age at exposure and at observation, and 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 populations with therapeutic (e.g., cervical cancer), diagnostic (e.g., tuberculosis), occupational (e.g., x-ray technologists) or environmental (e.g., to radon) exposures. Program members serve on committees advising the government and international agencies.

Results of studies suggest that (1) susceptibility to radiogenic breast cancer declines with increasing age at exposure, the dose response is linear, and risk remains for at least 50 years; (2) repeated exposure to relatively low radiation doses poses some future risk of breast cancer but apparently not lung cancer; (3) low-dose radiotherapy to treat uterine bleeding induces many more leukemias than high-dose radiotherapy to treat cervix, breast and other cancers, suggesting the importance of cell-killing in defining dose-response relationships; (4) radiotherapy for cervical cancer increases the risk of cancers of the rectum, bladder, vagina, stomach and thyroid; (5) diagnostic x-rays may not be causally related to leukemia or lymphoma but simply related to conditions that portend their development; (6) children irradiated for benign conditions are at risk of developing thyroid, skin, and brain neoplasia; (7) diagnostic x-ray workers in China are at high risk of leukemia; (8) approximately 10% of all lung cancer deaths may be due to indoor radon; (9) low-dose radioactive iodine does not appear to increase the risk of thyroid or other cancer, and (10) high natural background radiation does not appear to increase appreciably the risk of nodular thyroid disease.

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
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Elaine Ron	Senior Staff Fellow	REB	NCI
Dale Preston	Expert Statistician	REB	NCI
Seymour Jablon	Expert Statistician	REB	NCI
Zdenek Hrubec	Expert Statistician	REB	NCI
Charles W. Mays	Expert Radiobiologist	REB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Katherine W. Chen	Computer Programmer	REB	NCI
Michele M. Morin	Epidemiologist	REB	NCI
Peter Inskip	P-Authority	REB	NCI
William J. Blot	Chief	BB	NCI
Linda M. Pottern	Epidemiologist	EEB	NCI
Jay Lubin	Biostatistician	BB	NCI
Margaret A. Tucker	Chief, Family Studies Section	EEB	NCI
Frederick P. Li	Chief, Clinical Studies 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 after exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; (3) 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; (4) to conduct case-control and follow-up (cohort) studies of cancer risk in patient populations given diagnostic or therapeutic radiation alone or in combination with cytotoxic drugs and other forms of treatment; (5) 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; and (6) to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities.

Methods Employed:

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.

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 Union. Int. Cancer. 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. 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 of 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. Eighteen medically irradiated populations are currently under study: women irradiated for cervical cancer, uterine corpus cancer, benign gynecologic disorders, infertility, breast cancer and non-Hodgkin's lymphoma; 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, scoliosis, or heart disease; 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 was 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 was expanded through the collaboration of 15 population-based cancer registries. Approximately 200,000 women with cervical neoplasia have been studied. The cancer registry cohort studies have been completed, and detailed case-control studies have been 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, have been evaluated by radioimmunoassay techniques. Chromosome aberrations in circulating lymphocytes have also been 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 was completed. Clinical examinations were performed on over 1,000 irradiated and surgical patients 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 included the evaluation of serum calcium levels and plasma thyroglobulin concentrations. Chromosome aberrations in circulating lymphocytes were also investigated 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 continued 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 was developed in Israel to evaluate whether the risk of thyroid neoplasms associated with a low radiation dose (0.09 Gy) 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 biochemical studies along similar lines have been initiated to evaluate observed excesses

of skin cancer. Irradiated and non-irradiated patients with skin cancer are being examined by a dermatologist. The physician is determining the presence and location of nevi and evaluating skin and eye color as well as other risk factors for skin cancer.

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. Medical records have been abstracted on cases and matched controls to quantify the risks associated with radiation or chemotherapy treatments. Collaborative dosimetry support is being provided for a similar investigation conducted in the United Kingdom.

5. New cohorts of women who received radiotherapy for benign gynecological disorders (BGD) in Massachusetts, New York, Rhode Island, and Connecticut 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, is being investigated, as will the unexpected reduction in breast cancer risk previously associated with irradiation for BGD in postmenopausal women. Chromosome studies are being conducted and findings will be contrasted with data from the international cervical cancer study.

6. Two population-based case-control studies were 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 were matched to each case. A parallel study in Denmark evaluated 129 cases of leukemia following breast cancer and 258 matched controls (1945-1980). Medical records were abstracted and individual bone marrow doses estimated. Analyses of the dose-response relationship between the radiation dose to active bone marrow and subsequent leukemia risk have been completed for the Connecticut study.

7. 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 perhaps for the lung, radiation risks for these sites are not well defined.

8. Cancer mortality in a cohort of 860 women who received pituitary and ovarian x-ray therapy (mean tissue dose: 0.90 Gy and 0.65 Gy, respectively) between 1925 and 1960 for the treatment of infertility and menstrual disorders in New York 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. Data collection for a cohort of 1,200 infertile women similarly treated in Israel has been completed. Statistical analysis of cancer incidence among the Israeli population is underway. Organ doses will be calculated.

9. There has been growing concern about the adequacy of the standards presently used to regulate exposures to neutrons. This concern was increased when it was learned that the study of the A-bomb survivors would yield little information on neutron effects. There are currently no data on the risk of cancer associated with neutron exposures in humans. For this reason, we are conducting a feasibility study for a multi-center epidemiologic study on patients treated with neutron therapy. Radiotherapists from over 23 centers report treating more than 12,000 cancer patients. It is estimated that at least 2,500 patients have survived over 2 years and would be eligible for study. Five neutron treatment centers have been visited and all have expressed their willingness to collaborate. A pilot study of over 500 neutron patients who have survived 2 years or more was initiated at Cleveland Clinic and M.D. Anderson Hospital. Data abstraction is now in progress and radiation organ doses will be estimated for each patient. A chromosome study of circulating lymphocytes obtained from newly treated and 2-year survivors of neutron therapy is now underway to evaluate the effects of high-LET radiation.

10. Two studies are being conducted among women treated for cancer of the uterine corpus to evaluate the dose-response relationship between radiation dose and the risk of second primary cancer. A case-control study identified over 230 cases of leukemia following uterine corpus cancer from 9 cancer registries in the United States, Canada, and Europe. Four controls per case were selected among uterine corpus cancer patients who did not develop leukemia. Detailed medical records will be abstracted and the radiation dose to the active bone marrow will be calculated for each study subject. In a second phase of this study, a cohort study involving approximately 500,000 patients will be identified to evaluate the risk of second primary cancer following treatment for uterine corpus cancer by time since treatment and age at first treatment. The results of this study will be used to select additional organ sites which might be valuably pursued in a future detailed case-control or case-cohort investigation.

11. The Surveillance, Epidemiology, and End Results (SEER) cancer registries and the Connecticut Tumor Registry were used to evaluate the risk of breast cancer occurring 10 or more years following radiotherapy for Hodgkin's disease. The effect of age at exposure and time to occurrence were evaluated.

12. To improve and extend the data available on radiogenic thyroid cancer, a previously identified cohort of over 5,000 individuals who received radiation treatment between 1939 and 1960 for enlarged tonsils and other benign conditions of the head and neck is being evaluated. Clinical and radiation therapy data were abstracted from the medical records of 5,054 patients who received at least one course of 200 kVp

radiation at Michael Reese Hospital in Chicago. Detailed data regarding method of tumor detection, tumor size and location were abstracted for over 1,000 patients known to have had a thyroid neoplasm. Medical physicists at M.D. Anderson Hospital have estimated organ doses for over 3,000 patients. A pilot study to assess the feasibility of tracing individuals lost-to-follow-up indicates that the tracing rate can be improved to approximately 80%.

13. To derive more understanding of radiogenic thyroid tumors and host susceptibility, we are reanalyzing data from 8 major studies (6 cohort and 2 case-control) of radiation-associated thyroid neoplasia. The basic data are being analyzed in parallel using identical categories and definitions where possible. Additional organ dose determinations are being made by medical physicists so that the analysis will include detailed uniform dose data. The effect of sex, age at irradiation, ethnicity, dose-response and if possible, dose fractionation will be evaluated as well as interactions among these factors.

Populations receiving diagnostic irradiation are described below.

14. 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 continued in Sweden. This research is based on a nationwide registry of more than 100,000 twins born between 1926-1967, among whom about 100 cases of verified childhood cancer have been found. Two twin controls have been selected for each case. Prenatal and early postnatal x-ray exposures have been determined through searches of hospital and prenatal clinic records.

15. 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. Cancers of the breast, lung, esophagus and thyroid are of particular interest. Studies are being conducted in Massachusetts and Connecticut to clarify further the carcinogenic effect of multiple low-dose x-ray exposures in both men and women. A collaborative analysis was conducted on data from the Canadian study of tuberculosis patients.

16. Using the resources of prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, 1,256 cases of leukemia and lymphoma and 1,578 controls have been identified. Long-term histories of diagnostic x-ray exposures have been obtained for all subjects. The

possible association of leukemia and lymphoma with radiation dose to active bone marrow is being evaluated. Analyses have been completed.

17. A feasibility study of 1,030 women with scoliosis suggested a nearly two-fold increased risk of breast cancer possibly related to diagnostic x-ray exposure. An expanded study was initiated to provide new and detailed information on the age-specific risk of breast cancer following diagnostic radiation for scoliosis at an apparently sensitive age, to relate risk to important biological processes such as breast development and menarche, and to fully assess the effectiveness of low-dose x-rays given frequently over a period of several years in causing breast cancer. About 6,000 women from approximately 12 different institutions will be enrolled for study. All cancers will be evaluated, but emphasis will be given to breast, leukemia, lung, and thyroid cancers.

18. A feasibility study of cancer risk in children who received multiple chest fluoroscopies during cardiac catheterization was completed at four hospitals which were at the forefront of cardiac catheterization in the early 1950s. This study evaluated the adequacy of exposure data and length of follow-up time. Rosters of patients will be compiled for possible study in the future. Subsequent risk of leukemia, breast cancer, and thyroid cancer would be evaluated. Additional feasibility work is being conducted in England and Holland to learn whether a sufficiently large sample might be available for study.

19. Analysis of a study of childhood cancer in relation to prenatal irradiation has continued. Childhood cancer deaths (n=1,044) in the period 1960-69 among children who had been born in military hospitals were identified in a study conducted by the Medical Follow-up Agency, National Academy of Sciences. Two control births for each child were chosen from the same hospital of birth, born as near in time to the day of birth of the case as possible. The virtues of this study design were that (a) information concerning radiation exposures would be available in the hospital records; there would be no need to rely on statements of uncertain reliability made years later by parents; (b) information about the parents would also be available in the records--data related to social class, such as military rank and education, history of previous pregnancies and their outcomes, parental ages, etc.; and (c) the decision to do pelvimetry or other radiological procedures would, in a military hospital, not be influenced by economic constraints, i.e. ability to pay for the procedures. The data file is now being reviewed to determine whether any evidence of bias in control selection remains. If not, analysis will proceed. In any case, useful information will be obtained concerning the relation of such factors as parental education, age, social class (as reflected by military rank), and others, to the chance of one or another form of cancer developing in an offspring.

Populations receiving isotopes are described below.

20. A study to evaluate the carcinogenic risks associated with diagnostic and therapeutic exposures to radioactive iodine among 60,000 patients in Sweden is nearing completion. A second follow-up of patients originally identified in the National Cooperative Thyrotoxicosis Therapy Follow-up Study (TT Study) is continuing. Morbidity and mortality data are being collected on about 23,000 persons treated by radioactive iodine (I-131) and 12,500 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 further studies in this area are warranted. In this regard, a new study of the carcinogenic effects of diagnostic I-131 was initiated in Israel and Slovenia, Yugoslavia. Together the two cohorts will include approximately 60,000 persons.

21. 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 I-131 therapy for hyperthyroidism. They developed palpable thyroid nodules one or more years after I-131 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, have located these patients and invited them to return to the clinic for an examination of the thyroid gland. The final clinical diagnosis will be analyzed as a function of I-131 dose, type of hyperthyroidism, age at first treatment, and duration of follow-up to assess the risk of thyroid disease following I-131 therapy.

22. Nine hundred West German patients treated for bone disease with radium-224 are being followed for late effects.

23. Patients in Denmark given radioactive Thorotrast during cerebral angiography for epilepsy are being evaluated for the later development of liver cancer and leukemia.

Other projects are intended to strengthen inferences from studies of medically irradiated populations in general.

24. 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,

children irradiated for tinea capitis, persons with leukemia and lymphoma who received diagnostic x-rays, persons exposed to multiple diagnostic x-rays for monitoring the progression of scoliosis, children treated with radiotherapy for cancer who subsequently developed a second malignancy, and women treated with radiation for breast cancer who subsequently developed a second breast cancer. Determinations are ongoing for women irradiated for breast cancer, benign gynecological disorders, infertility, or endometrial cancer who subsequently developed leukemia; persons irradiated for treatment of peptic ulcer; and, cancer patients treated with neutrons.

25. Biochemical and cytogenetic studies: The value of cytogenetic aberration data as a biological dosimeter in persons with partial-body irradiation is being explored in six medically-irradiated populations in collaboration with cytogeneticists at Oak Ridge Associated Universities. The objectives are: to evaluate chromosome aberrations as biological dosimeters for partial-body radiation exposure; to contrast the dose-response relationships of the frequency of aberrations per unit dose with similar dose-response data on cancer risk in the same irradiated populations; and to investigate the influence of age, sex, fractionation of dose, duration of time since exposures, and total dose on the yield of chromosome aberrations, through comparable analyses of different data sets. Populations being evaluated include cervical cancer patients, tuberculosis patients, persons exposed as infants for enlarged tonsils or thymic glands, women irradiated for benign gynecologic disease, and cancer patients treated with neutrons. Chromosome aberrations have been analyzed in women residing in areas of high and normal background levels of natural radiation in China. 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 over 350 cervical cancer patients 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, serum samples have been 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 was initiated between the Radiation Epidemiology Branch (REB) 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 undoubtedly 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 or under way with respect to the breast, lung, and thyroid. Senior investigators from RERF and the REB jointly prepared a platform protocol for incidence studies, which laid out basic principles of study design and analysis, and arrangements for enlisting the collaboration of individual pathologists who would assume primary responsibility for case acquisition and review. This protocol was adopted recently by RERF and accepted by the local pathology associations of Hiroshima and Nagasaki as the basis for future collaboration on studies of this type. An important part of the new program is an address data base for all living LSS sample members, from which denominators can be constructed for cases ascertained from local and distant sources such as tumor and tissue registries. Negotiations with local and national government agencies for access to information for this data base have been proceeding smoothly.

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. A total of 300 cases was reviewed in two sessions in Grand Junction, Colorado, and Hiroshima. Reviews were also conducted in two stages, a blind review by individual pathologists, and a consensus review using television and multiheaded microscopes.

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-linear energy transfer 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 of a professional registry of over 200,000 medical x-ray technologists established in 1926 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 completed on over 103,000 active and inactive members to date; 6,000 have been determined to be deceased, and 4,500 have refused to participate in the study. Eighty percent 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 questionnaires to do so. An abbreviated telephone interview has been attempted with all questionnaire nonrespondents to obtain information on cancer incidence.

2. In collaboration with the staff of the Baltimore Gas and Electric utility company, a cohort study of nuclear power workers at the Calvert Cliffs plant was conducted. Follow-up of the employees was completed, and lifetime occupational exposures estimated. Both the regular utility company workers and contractor employees were evaluated. Using the historical dose files of the Nuclear Regulatory Commission and the plant records, dose estimates could be obtained for 94 percent of the workers.

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 400 women with lung cancer and 400 matched controls to determine the extent of this risk. A Swedish study, similar to the one in New Jersey, is also being completed. Pilot efforts have demonstrated the feasibility of obtaining alpha track detector evaluations of the residential radon exposures of these subjects and the reliability of this measurement method. The alpha track readings were found to be highly correlated with thermoluminescent detector measurements, although systematically they produced somewhat higher values. Alpha track exposure evaluations have been extended to the rest of the study subjects. In all, 200 cases and 400 controls have been included. In China, a radon component was added to a lung cancer case-control study in Shenyang. Approximately 300 women with lung cancer and 300 controls had passive detectors placed in their residences. Collaboration on a radon study of lung cancer risk in Missouri is continuing. The sample is being expanded to include 550 cases and 1100 controls.

4. A study of thyroid nodules associated with high natural background areas in China has been conducted in Guangdong province. Over 2,000 women over the age of 50 years were examined for thyroid abnormalities by four U.S. physicians. Blood samples for thyroid hormone levels and for chromosome analysis have been analyzed.

5. The possible health effects of electromagnetic radiation are the subject of much uncertainty and disagreement. The suggestion of effects in children is of particular interest. In this regard, and in collaboration with the Biostatistics Branch, a measurement protocol has been developed that will be appended to a nationwide case-control study of childhood leukemia.

6. Cancer incidence among 27,011 diagnostic x-ray workers was compared to that of 25,782 other medical specialists employed between 1950-1980 in China. The radiation workers included both radiologists and technicians. The comparison population consisted of 12,446 surgeons,

10,995 physicians, 2,306 otolaryngologists, and 35 other specialists working in the same hospitals during the same time period, but who did not use x-ray equipment in their work. Overall mortality and cancer incidence were determined through December 31, 1980.

7. Studies of mortality in the vicinity of nuclear installations in England suggest that risks of childhood leukemia may be increased in certain of those locations. To clarify this matter, a nationwide survey of mortality around nuclear reactors in the U.S. was initiated. All commercial power generating and Department of Energy weapons and research facilities that were ever operational and that exceed a nominal power output have been included. Mortality of counties with or near such nuclear installations is being compared over time with the mortality of counties without such facilities, but chosen for their similarity with the reactor counties on demographic and socioeconomic factors. Any differences found will be evaluated in detail in relation to the start-up date of reactor operation and other secular changes between the affected counties.

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 and breast cancer incidence data from several exposed populations. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of baseline and excess risk are compared, as well as integrated risk over the entire period of observation. Analysis of the potential risks of lung cancer associated with indoor radon gas has been conducted. 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 National Aeronautics and Space Administration, the International Commission on Radiation

Protection, the World Health Organization, and the National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiation (BEIR V).

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 possible risk of second primary cancers associated with irradiation in breast-conserving therapy, the risk of lung cancer associated with radon, 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.

G. Workshop. An International Workshop on Risks from Radium and Thorotrast was held in October 1988. This workshop was jointly sponsored by the National Cancer Institute, the Commission of the European Communities and the Department of Energy. A major objective was to understand the mechanisms and evaluate the risk coefficients for cancers induced by internally deposited alpha-particle emitters in German patients injected with radium-224, the U.S. and British radium dial painters, and patients injected with Thorotrast. The peer-reviewed proceedings are scheduled to be published in late 1989 in the British Journal of Radiology. A smaller workshop on the effects of diagnostic doses of radioactive iodine was also held this year, including investigators from Sweden, Israel and Yugoslavia.

Major Findings:

A. Medical Exposures.

1. The international study of 200,000 cervical cancer patients treated with radiation and/or surgery linked new cancers to radiation which included cancers of the rectum and vagina. Very high doses, on the order of several hundred gray, were also found to increase the risk of cancer of the bladder and possibly uterine corpus, bone and non-Hodgkin's lymphoma. Doses on the order of several gray increased the risk of stomach cancer and possibly kidney cancer, but not pancreatic cancer. Doses greater than 6 Gy to the ovaries resulted in a 23% reduction in breast cancer risk. No overall risk was found for direct exposure to the breast, despite an average dose of 0.31 Gy; however, a weak suggestion of a dose response was apparent among women whose ovaries had been surgically removed. Radiation also was not found to increase the overall risk of cancers of the small intestine, colon, connective tissue, vulva, and Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia. A twofold risk of radiogenic thyroid cancer, however, was suggested following an average dose of 0.10 Gy.

2. A study of 13,385 tuberculosis patients treated between 1915-1954 in Massachusetts, many of whom received multiple chest fluoroscopies during pneumothorax treatment, indicates that repeated relatively low radiation doses pose a long-term risk of breast cancer, but not lung cancer or leukemia. A record-linkage study of tuberculosis patients in Connecticut indicated a risk of breast cancer among young women that could be linked to multiple chest fluoroscopic exposures. An analysis

of the mortality data from the Canadian tuberculosis study confirmed earlier findings on the linearity of the dose-response for radiogenic breast cancer and the decreasing risk associated with increased age at exposure.

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 and other neural tumors, 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 at only 0.24 Gy. Risk estimates derived from a mailed questionnaire, however, were much higher than those from a clinical examination, suggesting that questionnaire studies might be misleading due to underascertainment of disease among nonexposed populations. The increase in stable chromosome aberrations in the irradiated tonsil patients was significant compared to surgically treated subjects.

4. Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased stable aberrations were detected up to 40 years after exposure, indicating that radiation damage can persist for extremely long periods of time. The stable aberrations in cervical cancer patients was 50% to 75% lower than rates observed for atomic bomb survivors or ankylosing spondylitis patients, despite the much higher average doses received during radiotherapy for cervical cancer. These data support the notion that high doses to small volumes of tissue result in cell death or inviability that must deplete the pool of cells available for aberration evaluation. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients given localized high-dose radiotherapy is the result of cell-killing effects of radiation.

5. The Swedish study of the relationship between prenatal x-ray exposure and childhood cancer produced results parallel to those for the Connecticut twin sample and other research. Childhood cancer risk, particularly that of leukemia, was elevated after irradiation, although the increases were not statistically significant. This outcome is consistent with the low exposures experienced by these subjects and suggests that the developing fetus may be as sensitive to radiation exposure as previously suggested. 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, particularly since this group is supposedly heavily exposed to prenatal x-rays. This deficit of risk of cancer in twins will also be investigated in the Swedish sample.

6. A small but significant risk of breast cancer was linked to multiple diagnostic x-rays among 1,030 women with scoliosis. There was an apparent dose response with risk being concentrated among women receiving the highest number of exposures and followed for the longest time. The data suggest that adolescence and the time of breast development, are especially vulnerable times to the carcinogenic effect of radiation.

7. A population-based study of women irradiated for Hodgkin's disease found a fourfold risk of developing breast cancer 10 or more years after initial treatment. Eight of the 9 breast cancers developed in women irradiated at ages under 40, including 4 women exposed in their teens. These results suggest that women receiving radiotherapy for Hodgkin's disease at a young age should be carefully monitored for late occurring subsequent breast cancer.

8. A population-based case-control study in Connecticut found that there was little evidence that radiotherapy for breast cancer increased the risk of leukemia. Local radiation doses to each of 14 bone marrow compartments for each patient were reconstructed; the dose averaged over the entire body was 5.3 Gy. There was no indication that risk varied over categories of radiation dose. These data exclude an association between leukemia and radiotherapy for breast cancer of 2.2-fold with 90% confidence, and provide further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue.

9. A diagnostic x-ray study was conducted within two prepaid health plans. Over 30,000 x-ray procedures were abstracted from hospital records and categorized, eliminating the possibility of response bias associated with interview studies. No association was found for chronic lymphocytic leukemia. For all other forms of leukemia combined, there was a significant increase in risk with increasing number of x-rays; however, this trend progressively diminished when x-rays near the time of diagnosis were excluded. The findings for non-Hodgkin's disease were similar. These data suggest that x-rays might not be causal factors but simply related to conditions that portend the development of leukemia or lymphoma.

10. A twofold risk of leukemia was observed among 4,483 women irradiated for benign menstrual bleeding an average of 26 years ago. Risk was highest 2 to 5 years following irradiation and among women older than age 55 years at treatment.

11. No excess of thyroid cancer, nor any other cancer, was found among 35,000 Swedish patients given diagnostic doses of I-131.

12. Among 900 West German patients who received high alpha-particle doses from radium-224, there were 56 bone sarcomas observed versus 0.3 expected (4.2 Gy average skeletal dose). There were 6 liver cancers observed versus 1.2 expected (1.4 Gy liver dose) and 14 breast cancers observed versus 6.1 expected (unknown breast dose). Although the alpha particle dose to the red marrow was about 2 Gy, there was no excess of

particle dose to the red marrow was about 2 Gy, there was no excess of leukemia compared to that in nonirradiated patients with the same disease. The possibility is being explored of extending these investigations to radium-224 patients in East Germany.

13. Radioactive Thorotrast was linked to high rates of liver cancer and leukemia among Danish epileptics. An excess of lung cancer might be related to the low levels of thoron gas emitted during the decay process.

B. Atomic Bomb Survivors.

1. Preliminary findings from a case-control study of breast cancer suggest that the usual factors related to reproductive history that predict breast cancer risk in other populations operate similarly in the A-bomb survivor population. A marked exception is that a lengthy history of breast feeding is associated with substantially reduced risk, an association that has been seen in only a few other populations. On the other hand, neither early age at menarche nor late age at menopause appeared to carry any excess risk, a result somewhat at variance with those in other populations. A more remarkable finding is that early age at first delivery, which is associated with reduced risk, appears to interact multiplicatively with radiation dose; that is, the excess risk associated with radiation exposure appears to be greater among nulliparous women, and women who first gave birth at an older age, than among women whose first deliveries occurred in their late teens or early twenties. Radiation dose response was significantly greater among women exposed before their first delivery than among women exposed at similar ages but after their first delivery.

2. In nutrient assays of stored serum obtained in 1970-72, persons who later developed stomach cancer were found to have had significantly lower levels of soluble iron than controls. This result, which seems to contradict an earlier finding of higher iron levels among Taiwanese subjects who later developed liver cancer, could conceivably reflect blood losses from chronic internal bleeding, or some other, noncausal relationship. Assays of other nutrients, and hormonal assays comparing breast, endometrial, and thyroid cancer cases with controls, have so far failed to show any case-control differences.

3. A dose-response analysis of breast cancer incidence data using a revised dosimetry system (DS86) shows surprisingly little change from the corresponding analyses using the T65D system. Because average dose levels are somewhat lower under the new dosimetry, risk estimates are increased by about 40%. DS86 doses have also been obtained for the colon and rectum, and similar comparative analyses have been conducted. A 10% increase in estimated colon cancer risk per rad was obtained compared with the old dosimetry, while for rectal cancer no evidence of a dose response was found.

4. 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.

5. Papers have been written comparing the effect of the new dosimetry changes on risk estimates among the survivors of the atomic bomb. In terms of total kerma (essentially whole-body gamma plus neutron exposure), risk estimates are 75-87% higher with the new dosimetry. At an assumed constant relative biological effectiveness of 10 for neutrons, the effect of the dosimetry revision is to increase organ dose risk estimates, relative to those based on the old dosimetry, by 30% for nonleukemia and 80% for leukemia. The city difference in dose is no longer statistically significant. There is substantial question of the linearity in dose-response, in the sense of a leveling off at higher doses.

C. Occupational and Environmental Exposures.

1. Preliminary analysis of thyroid cancer risk among 80,000 x-ray technologists who responded to a mail questionnaire indicates a twofold risk compared to population expectation. However, the excess risk appears to be due to personal medical exposures rather than occupational x-ray exposures.

2. X-ray workers in China had a 50% higher risk of developing cancer than other specialists not frequently exposed to radiation during employment. Cancers linked to radiation work included leukemia, breast and thyroid, and possibly bone and skin. High risks of cancers of the esophagus and liver were not consistent with a radiation effect and might reflect differences between groups of hospital workers in social class, alcohol intake, dietary habits, and other risk factors. No excess lung cancer or multiple myeloma was observed. The excess leukemia followed a wave-like pattern, peaking 10-14 years after start of employment and decreasing to normal levels after 20 years.

3. The risk of radon-induced lung cancer among residents of single family homes in the U.S. was estimated using models recently developed by the National Academy of Sciences BEIR IV Committee. These models predict that approximately 14% of lung cancer deaths (about 13,300 deaths per year) may be due to indoor radon exposure. The attributable risks due to radon are similar for males and females and for smokers and nonsmokers, but higher baseline risks of lung cancer result in much larger numbers of radon-attributable cancers among males (approximately 9,000) and among smokers (approximately 11,000). Most of the contribution to the attributable risks arises from exposure rates below 4 pCi/l. As a result, if all exposure rates which exceed 4 pCi/l (approximately 8% of homes) were eliminated, the models predict that the annual lung cancer burden would drop by 4%, or by about 3,800 lung cancer deaths, in contrast to a maximum reduction of 14% if all indoor radon exposure was eliminated.

4. No risk of radiogenic thyroid tumors was found among 2,000 women in China who underwent physical examinations. Half of the women resided

in areas of enhanced natural background radiation due to monazite sands. The average thyroid dose was estimated to be between 0.08 and 0.18 Gy. More stable and unstable chromosome aberrations were detected in the women who lived in the high background area, however, the rates of aberrations were low for both groups.

5. Sixty-four counties have been identified where nuclear facilities are located that began operations prior to 1982. The facilities include all commercial power plants, all Department of Energy military reactors and fuel fabricating and reprocessing plants. In addition, forty-three counties were identified that, while not themselves containing a facility, account for a significant proportion of the area within ten miles of a facility; seven of these counties qualified with respect to two facilities. Three "control" counties were selected for each of the 107 "Study" counties. The total number of different control counties included in the study is 291; some counties were chosen as controls for more than one study county. The control counties were selected using a combination of characteristics such as population size, educational level, ethnic composition and average family income, to achieve as much comparability as possible with respect to baseline cancer rates. Comparisons will emphasize leukemia, especially childhood leukemia, but will not be limited to that disease. All comparisons will be controlled by calendar year to take account of the increasingly efficacious treatment of some childhood cancers in recent years. The observed number of deaths from various cancers in particular age and sex groups will be compared with the numbers expected on the basis of the rates in the control counties and in the entire U.S. Comparisons will be time-specific, as before the nuclear facilities became operational or afterwards, taking account of the necessary latent period for each cancer. Excesses found for particular plants will be correlated with the history of annual gaseous and liquid emissions from the plant to help distinguish excesses caused by radiation from the plants from excesses that are the result of chance.

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.

2. Development and documentation of AMFIT (a program for the analysis of grouped survival data using Poisson regression methods) and PYTAB (a production of complex person-year tabulations) have continued. Versions of these programs will be included as part of the REB-developed package of epidemiological programs for personal computers. These programs were used by the National Academy of Sciences' BEIR IV committee in their analyses of the risks associated with radon exposure and they are currently being used by the BEIR V committee as the primary tools for the analysis of data from a wide variety of studies of radiation effects.

During the past year significant improvements have been made to AMFIT and PYTAB. These improvements include generalization of the class of risk models which can be fit, procedures for automatic generation of design variables and interactions, enhanced data-handling capabilities, and integration into EPITOME. AMFIT was restructured in order to simplify the development of similar regression programs for epidemiologic data. AMFIT-like regression programs for use in the analysis of matched (PECAN) and unmatched (GELLO) case-control studies as well as ungrouped survival data using partial likelihood methods (PEANUTS) have been developed. These programs have a common user-interface and can be used to fit the same broad class of generalized risk models. Detailed examples and documentation of the commands for these programs has been prepared. The DATAB program has been enhanced to include the person-year computation features of PYTAB.

3. Preliminary copies of "Epitome: Epidemiologic Analysis with a Personal Computer" have been distributed. This REB-developed package of epidemiologic programs should be completed within the year.

4. Using data from the Japanese A-bomb survivors, the original Massachusetts fluoroscopy series, the Canadian fluoroscopy series, and the New York acute post-partum mastitis study, parallel analyses of breast cancer incidence following radiation exposure were carried out. These analyses suggested that there are significant differences in absolute risks per unit dose between the North American and Japanese data, but that relative risks were not significantly different between the cohorts. As in earlier analyses of these data, risk was found to be inversely related to age-at-exposure. The initial results suggested that relative risks were not constant over time; however, further work is needed to clarify this important issue. The results of these analyses have been used as the basis for the discussion of breast cancer risk in the BEIR V report. Results of these analyses have had an impact on interpretation of the Canadian data.

5. Non-stochastic epidemic models which allow one to examine the effect of voluntary confidential testing or other interventions on the spread of AIDS were developed in collaboration with other members of the EBP.

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CONTRACTS IN SUPPORT OF THIS PROJECT

ENERGY, DEPARTMENT OF (Y01-CP-80505)

Title: Studies on Radiation-Induced Chromosome Damage in Humans

Current Annual Level: $130,267

Person Years: 2.8

Objectives: To study radiation-induced chromosome damage in six different human populations, irradiated from 15 to 50 years ago. All six 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 five populations with respect to dose, quality of radiation, fractionation, age, and sex. The purpose is (1) to evaluate the usefulness of chromosome aberration frequency as a biological dosimeter for partial-body exposures, (2) to contrast the dose-response relationship of the frequency of aberrations per unit dose with similar dose-response data on cancer risk in the same irradiated populations, (3) to obtain insights into a biological effect that may be similar to radiation carcinogenesis, and (4) provide information about the relative biological effectiveness of 14 MeV neutrons in inducing chromosome aberrations in lymphocytes in vivo.

Methods Employed: Chromosomal aberrations are being determined and analyzed in 900 subjects selected from among six 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, persons irradiated for enlarged thymus glands during infancy, women irradiated for benign gynecologic disorders, and cancer patients treated with neutrons. About 50 nonexposed persons from each of these populations are selected as controls when possible. 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.

Major Contributions: To date, cultured blood samples (200 cells each) have been completed on 159 tonsil patients, 287 cervical cancer patients, 150 tuberculosis patients, 202 patients treated as children for enlarged thymus glands, 64 women irradiated for benign gynecologic disorders, and 15 cancer patients treated with neutrons. 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 or enlarged thymus gland. Age, sex, and smoking histories were controlled in the analysis. A significant dose-response was observed for stable aberrations in the tuberculosis patients who received multiple chest fluoroscopies many

years ago. Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased aberrations were detected up to 35 years after exposure, indicating that radiation damage can persist for extremely long periods of time. The percentage of aberrant cells among cervical cancer patients was only 3%, in contrast to 9% found among atomic bomb survivors, despite the much higher average doses received during radiotherapy. These data support the notion that high doses to small volumes of tissue result in cell death or inviability that must deplete the pool of cells available for aberration evaluation. When adjustment was made for cell-killing effects within the high dose pelvic area, the chromosome aberration frequencies and percent aberrations per unit dose overlapped for cervical cancer patients and atomic bomb survivors. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients given localized high-dose radiotherapy is the result of cell-killing effects of radiation.

SURVEY RESEARCH ASSOCIATES (NO1-CP-71096-01)

TITLE: Case-control Study of Residential Exposure to Radon

Current Annual Level: $100,000

Person Years: 3.0

Objectives: To evaluate the relationship between residential radon exposure and lung cancer in women.

Methods Employed: The contractor is providing technical, managerial, and clerical support for a population-based case-control study of non-smoking incident female lung cancer cases identified in the Missouri Cancer Registry. Two controls are being selected for each case by sampling the Missouri drivers license registry for cases under age 65 and the files of the Health Care Financing Administration for those age 65 and over. About 550 cases are expected to be enrolled between January 1988 and July 1991. Exposure to radon is evaluated by year-long measurements using alpha-track detectors which eliminate seasonal variation in the assessments.

Major contributions: The data collection instruments are being administered to cases and controls as new subjects are being enrolled. A rapid ascertainment system for new cases has been implemented which allows data collection to take place soon after diagnosis, before there is an appreciable loss through mortality. Residences of the subjects for the past 30 years are being surveyed. Radon detectors have been recovered from 1947 residences, about half of all of the residences that will be surveyed for this study. Response rates of 80% have been attained so far.

TEXAS, UNIVERSITY OF, M.D. ANDERSON HOSPITAL (NO1-CP-01047)

Title: Studies of Iatrogenic Cancer and Radiation Dosimetry

Current Annual Level: $220,000

Person Years: 3.45

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, cobalt-60 units, and neutrons 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 (1) studies of cancer following childhood cancer treatment with radiation, (2) leukemia and lymphoma following diagnostic x-ray procedures, (3) cancer following treatment for testicular cancer, (4) contralateral breast cancer following radiotherapy for an initial breast tumor, (5) cancer following radiotherapy for benign gynecologic disorders, (6) cancer following neutron therapy, (7) patients undergoing multiple x-rays for scoliosis, (8) leukemia following radiotherapy for breast cancer, (9) thyroid cancer following irradiation for enlarged tonsils and other benign head and neck conditions, (10) cancer following radiotherapy for tinea capitis, (11) patients undergoing heart catheterization, (12) cancer following radiotherapy for retinoblastoma, (13) cancer following irradiation for peptic ulcer, (14) women irradiated for benign gynecologic disorders, (15) women irradiated for infertility, and (16) leukemia following radiotherapy for endometrial cancer.

WESTAT, INC. (NO1-CP-31035)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $1,617,854

Person Years: 12.5

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) questionnaire preparation and tracing for the x-ray technologist study; (3) leukemia case-control study among breast cancer patients reported to selected SEER cancer registries; (4) Veterans Administration adjuvant drug study evaluations; (5) clinical trial evaluations of leukemia risk following breast cancer; (6) follow-up and tracing for the TB-fluoroscopy breast cancer studies in Massachusetts and Connecticut; (7) study of cancer following radiotherapy for infertility in New York; (8) study of second breast cancer following radiation therapy in Connecticut; (9) cohort study of children irradiated for enlarged tonsils in Chicago; (10) cohort study of 3,000 children with lymphoid hyperplasia who were treated with and without radiation in Boston; (11) feasibility study of workers in China exposed to neutrons; (12) feasibility study of nuclear power workers; (13) study of new cancers following treatment for retinoblastoma; (14) hormonal and chromosomal studies of cervical cancer patients; (15) second cancers following treatment for non-Hodgkin's lymphoma; (16) a feasibility study of cancer risk in children who underwent cardiac catheterization; (17) a study of radon exposure and lung cancer risk in New Jersey; (18) follow-up study of children irradiated for enlarged tonsils in Chicago; (19) study of leukemia following radiotherapy for uterine corpus cancer; (20) tracing support for studies of women receiving radiation treatments for benign gynecologic disorders; (21) feasibility study of patients treated with neutrons; (22) tracing support for study of persons in Chicago irradiated for peptic ulcer; (23) mortality survey of persons living in counties near nuclear facilities; and (24) directing the management of all tracing activities of the Epidemiology and Biostatistics Program.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-31036)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $383,812

Person 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 and a nationwide follow-up study of patients treated for hyperthyroidism. 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 were 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: The major effort of this contract has been the support of 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 was completed in December 1986. Although based on only 11 breast cancers occurring in some 1,000 women, this represented a nearly twofold excess. These results prompted the expansion of the study to include more centers so as to obtain a large enough sample to address this issue adequately.

Extensive support was also provided in location and determination of vital status of patients from the hyperthyroid follow-up study. Medical record abstraction has been completed at all 19 hospitals. Tracing and vital status ascertainment has been completed at 15 of the 19 hospitals (location efforts are ongoing for the patients from the Mayo Clinic and the three hospitals in New York). Final vital status has been determined for about 60% of the patients in the study, another 9% are presumed deceased (pending death certificate confirmation), and 10% have been lost to follow-up.

WESTAT, INC (NO1-CP-71107)

Title: Breast and Other Cancers Following X-Rays for Scoliosis

Current Annual Level: $478,598

Person Years: 4.1

Objectives. The main objective of this contract is to obtain managerial, technical, and clerical support for an expanded epidemiologic follow-up study of patients treated for scoliosis, which will be directed by the Radiation Epidemiology Branch, National Cancer Institute. The contractor will function in a supporting role, carrying out specific tasks, and will not engage in independent research.

Methods Employed: A cohort of approximately 6,000 additional women with scoliosis has been identified and cancer incidence and mortality will be determined from medical records, questionnaires, and death certificates. Demographic, medical and family history, x-ray exposure, and location information will be abstracted from the patient records. The number and types of x-ray films taken for each patient will be identified and tabulated. Radiation dose estimates will be developed under a different contract (NO1-CP-01047), based on information contained in the patient medical record and data from the x-ray films and machine parameters. Tracing of subjects will be

conducted using resources of both the NCI and the support services contractor. It is estimated that about 35% of the tracing will be conducted through NCI resources and 65% through the contractor resources. Once a person has been found, a questionnaire will be mailed to obtain information on medical history, family history of breast cancer, tumor diagnoses, and reproductive factors (e.g., ages at first pregnancy, menarche, and menopause). Death certificates will be collected for all decedents. Reported cancers will be validated by obtaining hospital discharge summary, pathology, surgery, or autopsy reports.

Major Contributions: Site visits have been made to the major clinics in the United States which have treated scoliosis patients for at least the past 30 years. It will be necessary to pool populations from about 12 different hospitals and clinics to obtain a sufficient sample size. Clinicians from each of these institutions have indicated a willingness to participate, and Institutional Review Board clearances are currently being sought. The medical record abstract forms and questionnaire have been modified based on the experience of the pilot study and information obtained during the site visit. Procedures for assessing x-ray exposure and evaluating stage of biological development at exposure have been established, and training materials have been developed. Abstractor training and data abstraction are ongoing.

INFORMATION MANAGEMENT SERVICES, INC. (NO1-CP-61006)

Title: Biomedical Computing Support for the Radiation Epidemiology Branch

Current Annual Level: $337,911

Person Years: 5.0

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 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; (8) cancer risk in tuberculosis patients; (9) cancer risk in scoliosis patients; (10) cervical cancer patient studies; (11) studies of radiation-induced thyroid neoplasms; (12) cancer following irradiation for tinea capitis; (13) chromosome damage following

irradiation; (14) evaluation of Generalized Iterative Record Linkage Systems (GIRLS) from Canada; (15) case-control study of leukemia and preleukemia following radiotherapy and chemotherapy for breast cancer; (16) cancer mortality among U.S. veterans in relation to smoking information obtained on questionnaires; (17) the hyperthyroid follow-up study; (18) county mortality near nuclear power facilities; and (19) dosimetry registry of radiation workers; among others. On average, approximately 20 studies or projects are supported during any given month.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05368-06 REB

PERIOD COVERED

October 1, 1988 to September 30, 1989

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	Chief, Family Studies Section	EEB	NCI
	L.B. Travis	Expert	REB	NCI

COOPERATING UNITS *(if any)*

Danish Cancer Registry (O. Jensen); M.D. Anderson Hospital (M. Stovall); Harvard Medical School (W. Moloney, H. Lisco); Connecticut Tumor Registry (J. Flannery)

LAB/BRANCH

Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.5	3.0	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 cancers 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. Z01CP04412-13 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-13 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.

Women with breast cancer who received chemotherapy are at an increased risk of leukemia; however, radiotherapy was not found to increase leukemia risk. Non-Hodgkin's lymphoma patients who received chemotherapy are at increased risk of bladder cancer. Alkylating agents to treat childhood cancer were not associated with an increased risk of thyroid cancer. Commonly used anti-convulsive drugs to treat epilepsy were not found to increase the overall risk of 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
Michele Morin	Epidemiologist	REB	NCI
Martha Linet	Medical Staff Fellow	BB	NCI
Margaret A. Tucker	Chief, Family Studies Section	EEB	NCI
Robert N. Hoover	Chief	EEB	NCI
Joseph F. Fraumeni, Jr.	Associate Director	E&B	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. Z01CE04412-13 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CE04410-13 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 has been conducted in collaboration with the Division of Cancer Treatment. From a survey of NCI-funded protocols, a number of cancer treatment trials was 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) have also collaborated in these studies. Drugs being evaluated include: methyl-CCNU, BCNU, CCNU, cyclophosphamide, chlorambucil, 5-fluorouracil, nitrogen mustard, and others.

2. 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, bone cancer and thyroid cancer have been completed. Analyses for cancers of connective tissue and of the brain are ongoing.

3. 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 in Connecticut has been completed in which complete treatment details were abstracted from hospital and physician medical records for 20 cases and 60 matched controls. The study has been expanded to four additional cancer registries: Iowa, Detroit, Los Angeles, and Atlanta. Eighty-eight cases of leukemia and preleukemia following breast cancer have been identified and 264 controls have been selected. Drug-specific risks will be quantified and compared, and the dose-response relationship for the most commonly used alkylating agents, melphalan and cyclophosphamide, will be estimated.

4. 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.

5. The risk of commonly used drugs is being analyzed in a case-control study of 1,256 cases of leukemia and lymphoma and 1,578 matched controls using the resources of prepaid health plans in California and Oregon.

6. 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, in particular the National Surgical Adjuvant Breast Project, have been contacted to extend these investigations.

7. 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.

8. 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.

9. A study has been 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 have been linked with hospital lists to ascertain cancers.

10. The risk of second primary cancer was assessed among a cohort of 544 persons diagnosed with cutaneous T-cell lymphoma (mycosis fungoides and sézary syndrome) from the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registries.

11. Radiation dose-response information was evaluated in studies of multiple primary cancers in cervical cancer patients treated in 16 oncologic clinics and 17 population-based tumor registries around the world.

12. A study was begun to identify patients treated with chemotherapy for a first cancer that may be at increased risk of a second primary cancer due to cytotoxic therapy. Data from the SEER cancer registries are currently being analyzed. Seventeen first primary sites (those commonly treated with chemotherapy) are being screened for increased risks of subsequent cancers, in particular excess solid tumors appearing 5 or more years after initial chemotherapy exposure.

13. An extended follow-up of 1500 patients with brain tumors treated with a nitrosourea drug (BCNU - Carmustine) is being undertaken. New leukemias or "pre-leukemias" that might have occurred since the last follow-up will be identified. If new trials have been initiated, these patients may also be included in the extended study. The previous evaluation of this population found an increased risk of leukemia, although the results were based on small numbers. Because there is so little data available in human populations exposed to single-agent chemotherapy, in particular BCNU, the extended follow-up will make an important contribution to our knowledge of late effects.

14. Data from the SEER cancer registries are being analyzed to detect any increased risks of solid tumors in patients treated for non-Hodgkin's lymphoma.

Major Findings:

1. The risk of secondary thyroid cancer following childhood cancer therapy was found to be largely due to radiotherapy for the initial primary cancer; no elevated risk from exposure to alkylating agents was suggested.

2. 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.

3. 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 first appeared two 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).

4. New cancers linked to radiation following treatment for cervical cancer included the rectum (RR=1.8), vagina (RR=2.7) and possibly the cecum (RR=1.5). Among cervical cancer patients with ovaries intact, radiotherapy for cervical cancer was linked to a significant 35% reduction in breast cancer risk, attributable to a cessation of ovarian function. Among the women without ovaries, there was a slight increase in risk (1.07), and a suggestion of a dose-response.

5. The frequently observed protective association of breast cancer with pelvic irradiation may be due, in part, to a decrease in estrone, testosterone or androstenedione--secondary perhaps, to adrenal irradiation.

6. A screening of 150,000 cancer patients treated with chemotherapy and reported to population-based cancer registries is being undertaken to identify possible increased risks of second cancers that may be due to their initial treatment. Preliminary findings suggest that acute leukemias are increased following chemotherapy for small cell lung cancer, breast cancer, ovarian cancer, testis cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma. Bladder cancer is elevated following chemotherapy for breast cancer, non-Hodgkin's lymphoma, and multiple myeloma. Lung cancers are in excess following non-Hodgkin's lymphomas and chronic lymphocytic leukemia. Patients receiving chemotherapy for ovarian cancer and chronic lymphocytic leukemia experience increased risks of subsequent colon cancer.

7. A twofold risk of bladder cancer following chemotherapy for non-Hodgkin's lymphoma was observed. Risk increased over time and reached 8-fold for 10-year survivors.

8. Among 544 patients with a first primary tumor reported as cutaneous T-cell lymphoma, a second cancer developed in 35 (6%), yielding a significantly elevated risk of 1.7. Excess second cancers of the lung may be due to their altered immune status and/or cancer therapies. The increased frequency of second colon cancer may provide a clue to common exposures or susceptibility mechanisms between these two sites.

9. Epileptics who received heavy and continuous exposure to anti-convulsive drugs, such as phenobarbital, were not found to be at overall increased risk for cancer development.

Publications:

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ANNUAL REPORT OF

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

October 1, 1988 through September 30, 1989

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 grants, cooperative agreements, and extramural contracts focused on epidemiology and biostatistics. The Branch strives to promote 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.

Biometry and Genetic Epidemiology: This program is primarily composed of research grant activities, although interagency agreements are being utilized specifically to determine the feasibility and cost effectiveness of various means of linking existing data to create an extramural epidemiologic resource. The grant program includes areas of theoretical biostatistics, genetic research and computer science. The areas are not discrete; most projects involve scientists from at least two. The common goal is to apply the three disciplines to foster understanding of cancer etiology. Any given theoretical biostatistical project has as its major goal the development of analytical techniques to improve clinical trials and risk assessment or to facilitate delineation of apparent gene-environment contributions to diseases and extrapolation of environmental exposure from species to species and from high to low dosages.

Epidemiology: The primary funding for this program area, also, is research grants; in addition, it administers the Epidemiology Small Grants Program. 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 Branch places special emphasis on biochemical epidemiology in an attempt to stimulate collaborative studies between epidemiologists and laboratory scientists. To achieve this aim, the Program issued a request for cooperative agreement applications for research designed to develop, validate and apply laboratory-based biochemical markers of human exposure and susceptibility for use in cancer epidemiologic studies. Eight new studies resulting from this initiative were funded this year, in addition to the seven studies under continuing support that resulted from our prior initiative. Investigators funded under these initiatives ordinarily meet annually to discuss progress.

The third in a series of workshops for investigators funded under the RFA, "Obesity and Cancer Risk in Women," was sponsored by the Division in March of this year. Consultants with special expertise in obesity research and investigators planning epidemiologic studies relating to hormones and cancer risk were included. The purpose of the workshop was to review and compare findings from different studies, and prepare for participation in a multi-Institute workshop scheduled for September 11-13, 1989 on the measurement and significance of body fat distribution. From the preliminary reports, there are suggestions that body fat distribution is a significant risk factor for both endometrial and post-menopausal breast cancer; that estrogen and androgen levels vary with fat distribution and the estrogen/testosterone ratio is significantly and similarly related to body habitus in males and females; that, while estrogen is clearly related to endometrial cancer risk, another hormone may be related to breast cancer risk; that estrone metabolites vary in physiologic activity with physiologically active metabolites binding irreversibly to cellular receptors and, although small in quantity for any given measurement, can exert a cumulative effect almost equivalent to estradiol; the metabolic pathway of estrone is influenced by environmental factors, including cigarette smoking in humans, dioxin and indole exposure in animals. Four of the workshop participants will prepare papers for presentation in September, to be concerned with the relationship between body fat distribution and sex steroids and glucocorticoids; body fat distribution and endometrial cancer risk; body fat distribution and breast cancer risk; nutrition and steroid hormones. These papers are to integrate published information as well as unpublished data to be provided by the investigators involved in the March workshop. Areas in which it is apparent at this time that additional investigation is needed are: measurement technology including fat analyses as indices of past dietary fat/carbohydrate ratios, better definition of the relationship between visceral fat and cancer, attention to the estrogen/testosterone ratio and disease risk, and meta-analysis of published and unpublished data. These and other issues are expected to become better defined in September. In view of the continuing importance of sex hormones and emerging interest in growth factors and cytokines, endocrinologic epidemiology has been identified as a special interest of the program in the revised referral guidelines.

AIDS Epidemiology: The Branch encourages new investigators to undertake studies of the incidence and etiology of malignancies associated with human immunodeficiency virus (HIV) infection. A Request for Applications (RFA) entitled "Epidemiologic Studies of HIV-Associated Malignancies" was issued in 1987 to attract new investigators to the study of HIV-associated malignancies. The RFA was planned to stimulate epidemiologic research in the following areas: (1) knowledge about the incidence of malignancies and premalignant conditions occurring in HIV-infected individuals; (2) understanding the specific mechanisms of carcinogenesis in HIV-infected individuals; and (3) understanding the relationships between immune status, genetic factors, HIV strains, co-infection with other viruses, AIDS treatments, and malignancy development. Nine applications were received and were reviewed by a special review committee in February 1988. Three outstanding applications were funded this year: a record-linkage study to establish the incidence of all malignancies in individuals with AIDS in San Francisco (159), a case-control study of the role of Epstein-Barr virus in the etiology of lymphoproliferations in children infected with HIV (78), and a nested case-control study of malignancies occurring in a cohort of homosexual men (57).

Small Business Innovation Research (SBIR) Program: The Branch continues to support the Congressionally-mandated Small Business Innovation Research Program designated to stimulate small business participation in Federal research and development projects. We have 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. During the period 1985-1987, the Program has awarded 13 Phase I contracts under eight topics. Four contracts successfully converted to Phase II. Three of these recently terminated, with at least one fast becoming a commercial success. FY 88 Phase I awards are just now being made for 11 contracts under six topics.

The Small Grants Program for Cancer Epidemiology was reannounced in August 1988 following intensive evaluation and approval by the DCE Board of Scientific Counselors. The program is serving a useful purpose especially for young investigators, recruiting doctoral students, fellows and junior faculty into cancer epidemiology. Ten of eighteen applications funded after the original announcement supported dissertation research and four were awarded to assistant professors. Presubmission contact with investigators gives staff the opportunity to encourage collaboration between epidemiologists and laboratory scientists interested in test development. Several changes increase the flexibility of the grants: allowable direct costs increased to $50,000 and the maximum project period increased to three years. Competitive renewal is permitted. The amended purposes of the program, all relevant to cancer epidemiology, include: planning a complex study; developing or validating a laboratory or statistical procedure; obtaining rapid funding; analyzing previously collected data, including meta-analysis; and resolving problems of methodology. During the last year, peer review of these applications has been conducted by telephone conference. This has been well received by both reviewers and applicants, while saving travel costs; a disadvantage is the heavy administrative burden for staff. Funds available for the small grants have remained level, resulting in fewer awards. Several unfunded applicants with excellent priorities were referred to the Wendy Will Case Foundation. The Wendy Will Case Foundation has one-time funding for applications under $50,000, and therefore, may be an excellent resource if the Foundation is interested in cancer epidemiology.

Estimates for Fiscal Year 1989 indicate that 190 grants funded for approximately $42,438,400 are monitored by the Branch. The grants monitored by the Branch in Fiscal Year 1989 are distributed among the various grant programs as indicated in Table I, below:

Table I
Distribution of Grants

Number (%)	Program	Funding	Proportion
7 (3.7)	R43/44	168,556	.4
7 (3.7)	R37	2,939,016	6.9
4 (2.1)	R35	2,592,737	6.1
7 (3.7)	R29	682,623	1.6
3 (1.6)	R13	35,000	.1
17 (8.9)	R03	462,434	1.1
11 (5.8)	P01	10,025,376	23.6
14 (7.4)	RFA	2,797,309	6.6
12 (6.3)	U01	1,410,848	3.3
107 (56.3)	R01	21,324,488	50.2
1 (0.1)	R15	.---	---

Total number of grants: 190 Total Dollars: $42,438,400 (approx.)

The allocation of Organ System projects to programs of the Institute added 1 program project (P01) and 17 traditional research project (R01) grants to the portfolio of the Branch. These include one relating to prostate cancer which terminated this year, three relating to colo-rectal cancer funded for $405,900 this year, and 14 concerning breast cancer, funded for $3,563,900.

The figures in Table I verify that R01 (traditional project) grants are most important to the Branch; these grants offer short-term support for discrete epidemiologic investigations and seldom exceed 5 years' duration. The next most important are the program project grants (P01's), which support multiple interrelated investigations and have a longer tenure. Almost one-fourth of the grants result from the special initiatives: R03's (small grants), RFA's (request for applications), and U01's (cooperative agreements). These account for only 11% of the funding and are made for periods of 3-5 years. Conference support grants (R13) and small business innovation grants (R43) are small components of the Branch activities. The long-term awards (MERIT, R37 and Outstanding Investigator Grants, R35) are of roughly equal importance in supporting the

research, but together these constitute only 7% of the grants and contribute only 13% of the funding. The significance of this factor is that staff of the branch are in very active contact with investigators, that a large proportion of the work concerns new ideas and contact with investigators during conceptualization of the research, and that the programs of the Branch are unusually susceptible to how funding conditions affect new applications. The bulk of R01 grants support case-control investigations and the most usual reason for a competing continuation application for these studies is a cut in funding level; since the projects rely upon a projected number of case observations, such cuts prolong the time required to satisfy data requirements for testing the main hypothesis and increase the overall cost of the research.

The recent changes in grants policy which delegate authority for approval to carry funds from one year of a grant to another are welcomed by epidemiologists and decrease the administrative burden for NCI staff. Almost all epidemiologic research projects are delayed in starting due to the extensive negotiations which are required to satisfy confidentiality concerns of hospitals, the usual source for identifying cancer cases.

The Branch supports 15 contracts, distributed as indicated in Table II.

Table II
Distribution of Contracts

Topic	Number	Funding (Dollars)
AIDS	3	1,000,000
NDI	1	209,139
Biometry	1	14,000
SBIR	11	549,000
Total	16	1,772,139

The NDI (National Death Index) study investigated the feasibility of adding mortality data for years prior to 1979 to the National Death Index. The cost was considered to be prohibitive. Alternate possibilities are now being explored intramurally. Other contracts included in the figures cited in Table II are discussed in the respective sections of this report (Biometry, AIDS and SBIR).

Of several events affecting the Branch this year, the loss of our highly respected Branch Chief to illness in mid-year has been the most inhibiting and has plunged us into intense sadness and evaluation of the staffing structure and organization of activities.

In general, the following discussion of program areas is restricted to research grants active in the period October 1, 1988 through May 15, 1989. Additional research grants will be funded during the remaining months of the fiscal year, but their individual focus and exact support level are uncertain at this time. We are able to estimate their impact on the budget at the Branch level, but not their impact on individual programs within the Branch.

BIOMETRY AND GENETIC EPIDEMIOLOGY

Description: The Extramural Biometry and Genetic Epidemiology Program is continuing its transition from a program of distinct areas of theoretical biostatistics, computer science, and genetics to a melding of collaborative work in genetic epidemiology and genetic mathematics. This phenomenon is due to recent technological advances in computer science and molecular biology, advances that have given researchers tools far beyond previously ambitious expectations. The computer, for example, is revolutionizing methods of data analysis. Powerful desktop workstations facilitate analytical/graphical exploration of moderately large data bases allowing epidemiologists/geneticists to examine their data and in effect let the data speak for themselves, i.e., multi-dimensional, multi-color graphic scatter plots. This presents a challenge to statisticians who must develop methodologies and software that will enable the users to distinguish what may appear to be interesting findings from what, in reality, may be statistical artifacts (17,64,69,84,101,126,180,209). Likewise, advances in molecular biology have given impetus to collaborative work in mathematical modelling. Statisticians are working with oncologists, geneticists and environmental scientists to assess interaction and delineate possible mechanisms of cancer etiology.

The program continues to support theoretical statisticians attracted to new analytic problems affecting public health, e.g., development of methods to predict future incidence rates of AIDS (18,86) and determine when clustering of cancer in geographic areas exposed to a carcinogenic agent can indeed be attributed to that agent (28,194,208). It is important to note that theoretical statistics in the program is related to existing biomedical/public health problems and is being approached such that once appropriate methodologies are developed, they will be made available to those who need them.

Clinical trials remain a topic of concern to a number of investigators (9,36,47,60,85,173,185,208). Now that matters of data collection, management, and analysis including the inherent problems of censoring, missing data and ethical considerations (sequential analysis and early stopping rules in order to get the best results in the shortest time using the minimum number of subjects) have been addressed in great detail, investigators are turning their attention to designing methods of treatment allocation to increase recruitment, innovative methods of drawing controls, and extension of analytic procedures to multiple endpoints and trials with multiple arms (9,47,60,190,194,208). Not to be overlooked are the data from clinical trials available for developing natural histories of various cancer sites. The latter has led to suggestions for collection of additional demographic, medical, environmental exposure, and genealogical data in future trials (156).

Research Accomplishments: The transition of the program to collaborative rather than mutually exclusive projects is perhaps most pronounced in the area of mathematical modelling (5,38,92,110,123,136,175,182). Early models were developed to explain the incidence rates of common adult cancers with incidence/mortality data generally coming from various population-based cancer registries. Although a number of models were proposed, because of growing interest in the two-stage carcinogenic model proposed by Knudson, and Knudson's long association with the DCE grant program, it will be used for purposes of this report (110). Knudson's model was based on his epidemiologic observations of

retinoblastoma in children which showed that a large proportion of cases occurred in those who had inherited an autosomal dominant retinoblastoma gene. In many cases there was a constitutional deletion of a critical piece of chromosome 13. Knudson suggested that the disease resulted from mutations at a specific site on both chromosomes 13 leading to homozygous loss of the function of a critical gene. The first mutation could be germinal (hereditary) or somatic (sporadic), whereas the second mutation was always somatic. Children with hereditary predisposition to retinoblastoma are born with cells of their retina requiring only one critical mutation for malignant transformation. The probability that at least one of the cells will suffer this critical mutation and become malignant is very high and hereditary retinoblastoma will appear to segregate in an autosomal dominant fashion on pedigree analysis, although the disease is recessive at the cellular level (because homozygous loss of gene function is required). At the time Knudson proposed this model (1971), it was known that the location of the retinoblastoma gene was on the long arm of chromosome 13 (110,176). Since then, molecular biologists have demonstrated that the salient features of the Knudson model for retinoblastoma are correct--the gene has been cloned (110).

The recessive oncogenesis (two-stage model) mechanism for malignant transformation has been substantiated in other human malignancies. The genes involved in these malignancies, of which the retinoblastoma gene is an example, are called regulator genes, tumor suppressor genes or anti-oncogenes. The discovery of the two classes of genes (oncogenes and anti-oncogenes) has been very important. Inappropriate activation of oncogenes could be a common pathway to carcinogenesis, as well as the inappropriate inactivation of anti-oncogenes. A stochastic model for carcinogenesis that incorporates these two classes of genes and explicitly considers the kinetics of tissue growth and differentiation has been generalized and applied to both epidemiological data in human populations and experimental data. Results are favorable in that expanded models incorporating time-related factors and carcinogenic exposure data have been consistent with a number of independent data sets, i.e., Wilms' tumor, colon and breast cancer in humans, and bladder and hepatocarcinogenesis in rats (1,2,14,21,80,92,194,208). Findings suggested by the model have been histologically verified. The model, as noted above, incorporates cell kinetics and views carcinogenesis as the end product of two critical specific, irreversible, rate limiting, and hereditary (at the level of the cell) genomic events (110).

It is because cancer is a disease of single cells rather than an entire organ that mathematical modelling of the disease process is feasible. The basic assumption is that a malignant tumor arises from single cells that have sustained a small number of critical insults to their genetic apparatus. The precise mechanism by which cancer kills an organism is by no means clear; however, it is clear that the severity of the disease is in some way related to the number of abnormal cells present. Caution must be taken in modelling cell populations without regard to distinguishing the biochemical or physiological differences among cells. It is overly simplistic to model tumor growth solely on cell (population) size for it has been shown that cells making up a tumor are heterogeneous with respect to proliferative capacity, nutritional status, oxygen content, and factors influencing response to carcinogens, chemotherapeutic drugs, and radiation. Even cells in an otherwise homogeneous population will respond differently to drugs and radiation depending upon their relative positions in their respective cycles. This is a critical matter, one in need of further

statistical, biochemical, and molecular input. Biologically realistic mathematical models of carcinogenesis present an important scientific approach to cancer risk assessment (209).

Vital regulatory decisions need to be made regarding permissible human exposures to various carcinogenic agents (5,40,85,106,136,156,209). Because relevant human epidemiologic data are rarely available, permissible levels of exposure are generally based on experiments in which animals are exposed to very high levels of a suspected carcinogen. It is being proposed that the two-stage (recessive oncogene) model be the model of choice in working with these exposure problems. There is, however, a crucial difference between human observations and animal experiments. In humans, cancer is a rare disease, whereas animal experiments are conducted under conditions such that a large proportion of the animals will develop tumors; many will develop multiple tumors of the same site. This necessitates the development of a new relative risk methodology. The Cox proportional hazard function which can be computed in human experiments, where cancer is rare, is invalid in animal experimentation. Further, if the methodology for determining relative risk in humans is to be dependent upon a methodology for determining relative risk in animal experiments, both inter-species variability and dosage extrapolation must be taken into account (110).

Several conditions complicate the comparison of control and exposed groups in tumorigenicity experiments. For example, tumor types vary in their lethality, with some causing death relatively soon after onset, and others having little or no effect on the risk of death. As a result of the large doses of the compound given in tumorigenicity experiments, the risk of death from non-tumor causes can be quite different in the control and exposed groups. An incomplete data score test has been devised to help resolve some of these problems. The results of this test show how the significance level for a data set changes as the lethality deviates, and, thereby, allows interpretations for a variety of intermediate lethalities. It may be possible to combine these results with beliefs about plausible lethality values either to reach a confident interpretation of the data, or to conclude that not enough is known about the true lethality to draw a firm conclusion. The incomplete data score test provides useful information, but the investigators caution that it is not the "end all" and that further work is required (85).

An automated technique for detection of mutational events that collectively alter the structure of a large number of proteins in both germinal and somatic cells has been developed (89). The method, two-dimensional polyacrylamide gel electrophoresis (2-D PAGE), resulted from the collaborative efforts of geneticists, biostatisticians, and computer scientists versed in artificial intelligence. Now at the point of implementation, the technique is being utilized by the investigators for high resolution separation of polypeptides of interest in cancer related research. The 2-D PAGE approach is designed to complement other approaches such as phenotyping of cell surfaces using immunologic probes, cytogenetic analysis to detect chromosome abberations and molecular biological investigations to detect alterations at the DNA level. Studies underway include: 1) estimating the change in somatic mutations due to chemotherapy in Hodgkin's disease and determining the fate of these mutations, and 2) estimating and comparing the germinal mutation rates in the general population and in the offspring of a high-risk group of cancer patients treated with radiation and chemotherapy (89).

The automated dietary data collection system under the direction of Dr. Buzzard has also reached the point of implementation. It resulted from the collaborative efforts of nutritionists, biostatisticians and computer scientists in much the same way as did the 2-D PAGE. The system is sophisticated, permitting dietary intakes to be assigned codes utilizing the customary United States Department of Agriculture nutrient data base and/or study/region specific nutrient data bases for nutrient calculation, yet saving data collection, editing and keying time. It is presently being used by both intramural and extramural cancer research projects at NCI as well as by other institutes, Federal agencies, and the private sector. Although the system is not as complete as the investigators had envisioned as a clinical research tool, it is, in its present form, well-suited for epidemiologic studies.

A theoretical statistical research project has as its focus two objectives: 1) development of statistical methods for monitoring the spread of HIV infection, and 2) development of methods for epidemiologic studies of AIDS with emphasis on natural history parameters of HIV infection (18). Work on the first is based on quantitative methods for projecting the course of the AIDS epidemic involving the use of back-calculation for obtaining short-term projections and lower bounds on AIDS incidence. AIDS incidence data together with estimates of the incubation period distributions are used to reconstruct the numbers of individuals previously infected. These results can then be projected forward to obtain short-term projections of AIDS incidence. A previous limitation of the method was that it did not account for new infections, thus the projections were lower bounds on future AIDS incidence. The investigator has extended the methodology so as to overcome this problem. The new approach involves fitting a step function model to the density of infection times (latency periods). The Centers for Disease Control have now incorporated these methodologies into their procedures for predicting the future trends of AIDS. As to the second objective, the investigator has developed statistical methods for the analysis of the natural history of AIDS in a hemophilia cohort. The method permits joint estimation of the effects of covariates both on the risk of disease and on the risk of progression to clinical disease once infected.

An increasingly common public health problem is the perception of disease clustering (28,194,208). In most cases the disease is cancer and the concern is exposure to a known or suspected carcinogenic agent(s). Etiologic agents can, and do, produce spatial, temporal or occupational clusters of cancer; however, to determine when a cluster of cancer is a true cluster requires new statistical methods. Detecting true clusters of rare cancers, e.g., angiosarcoma of the liver among men occupationally exposed to vinyl cloride is straightforward, but the common cancers present two problems. First, clusters may be obscured by the scattered occurrence of cases unrelated to the cause of the clusters. Secondly, clusters may be produced by factors unrelated to the disease process, such as variations in the overall population distribution or variations in the distributions of demographic subgroups at high risk of the disease. Statisticians are working to develop statistical approaches for detection of clusters. These methods will enable epidemiologists/public health officials to avoid costly epidemiologic studies unless the cluster is, in fact, a cluster. It is recognized that much innovative work is needed in order to provide a uniform solution to this problem.

Two interagency agreements, one with the Social Security Administration and the other with the Internal Revenue Service, have terminated. These agreements were to support efforts to develop a national resource (data tape) for the investigation of cancer in the workplace. At the present time, data from the studies are being looked at critically in light of overall worth and feasibility (229).

Projections: The program is contributing to the support of a conference, to be held this spring, which will address multidisciplinary approaches to developing a model for assessing the carcinogenic risk of humans from exposure to environmental agents (183). The conference will bring together experts in risk assessment, carcinogenic modelling, pharmacokinetics, and molecular epidemiology. It is through conferences such as this that quantitative (statistical/ mathematical) problems are identified and biostatistical investigators are encouraged to join with their counterparts from other sciences to formulate new projects. The transitory state of the program is, in effect, a result of such collaborative efforts.

It seems providential that new statistical problems will surface as biostatisticians continue to consult with other scientists and geneticists conducting oncologic research at cancer centers. It is vitally important that the statisticians remain on the cutting edge so that when a new analysis is called for an appropriate technique will be available.

The investigators in the program continue to be productive in their respective areas of expertise. Publications in refereed journals continue to appear in abundance, attesting to the productivity of the present grantees. There is every reason to believe this will continue.

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 and associated conditions; studies of the incidence, prevalence and mortality from human cancers; and examination of the geographic distribution 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, as well as basic epidemiologic research which may provide information essential to preventive intervention.

In order to improve the specificity and accuracy of research findings, the program supports methodologic studies that relate to the design, conduct and analysis of epidemiologic investigations, and that improve the capacity to distinguish contributions of multiple risk factors. This support includes the development and characterization of laboratory procedures. In 1982, a program in biochemical epidemiology was initiated to refine new measurement techniques and to encourage their subsequent use to study individual response to hazardous exposures, as well as to delineate high-risk groups. Thirty-three grants have

been funded in response to four special initiatives issued by this program. However, in the intervening time, analytic epidemiologic investigations have progressed so that improved techniques of estimating risk parameters are usually employed.

By and large, traditional research grants and program projects fund this epidemiologic research; however, since 1986, small grants have also been available for pilot projects, feasibility studies, test development and dissertation research support. To date, 24 small grants have been funded.

Research Accomplishments: Over one million women in the United States have had breast cancer diagnosed at some time during their lives and between 5 and 10 percent of these develop a primary cancer in the other breast. Women who reported breast cancer in any first- or second-degree relative have been found to be almost three times as likely to have a second primary breast cancer as women without that family history; the second cancer is more likely to be diagnosed within the first year and is also more likely to occur in women with a histologic diagnosis of lobular carcinoma. Reports of breast cancer research include: the association of breast fluid volume and hormone, cholesterol and lactose levels with proliferative breast disease; the biologic mechanisms underlying the association of benign breast disease with breast cancer; and the effects of dietary fat on estrogen metabolism.

For several years, fluids aspirated from the nipples of women who are neither pregnant nor lactating have been studied in an effort to understand how environmental exposures affect the breast and relate to the risk of breast cancer. Not all women yield breast fluid; this is especially true of Chinese and Japanese women who are at low risk of breast cancer. Women between 35 and 50 years of age, those with early onset of menses, and those who had lactated were more likely to have breast fluid. However, presence of fluid was not affected by the menstrual cycle, family history of breast cancer or prior fetal loss. While the ability to obtain fluid was not related to natural estrogen levels or the use of estrogen pills, much higher concentrations of estradiol and estrone were found in breast fluid than in blood serum. Women who had recently given birth or breast-fed their infants had lower estrogen levels, whereas women with benign breast disease had higher hormone levels in their breast fluid than most women. Lactose, a marker of secretory activity, was found in all breast fluid from women under 30 years of age, but in only about one third of samples from women over 35 years. The presence of lactose in both nulliparous and parous young women was indicative of the breasts' response to prolactin stimulation. Breast fluid varied from colorless through white, pale yellow, dark yellow and green to black. Only traces of lactose were found in the darker colored fluids. The proportion of women with dark colored breast fluid increased from 22% in women under 30 years to almost half of those from women in their fifties and was higher in women who smoked; sodium and potassium concentration increased with dark coloration. The proportion of Chinese and Japanese women with dark fluid was much lower than was true for other women. Color of fluid was not related to other breast cancer risk factors nor to the presence of either benign or malignant breast disease. Cholesterol, cholesterol 5,6-epoxides and their metabolite, cholestanetriol, were found in high concentrations in breast fluids. The oxides of cholesterol are toxic to cells and are reported to be mutagenic and carcinogenic in experimental animals. The histologic progression of breast epithelium from

normal to hyperplasia without atypical cells to atypical hyperplasia was associated with increasing concentrations of both cholesterol and cholesterol beta-oxide. Proliferative breast disease was 8.5 times as likely to occur in women with cholesterol beta-epoxide in their breast fluid as in women without detectable levels of this substance (133).

Only certain forms of benign breast disease are known to increase the risk of breast cancer. A 17-year follow-up of Nashville women with benign breast disease without cancer revealed that risk of breast cancer was not increased for women who received supplemental estrogens later than 1956, those who smoked or those who consumed alcohol. A histologic diagnosis of sclerosing adenosis increased the subsequent breast cancer risk in itself, and this diagnosis was frequently associated with the presence of other breast cancer risk factors: to wit, the presence of histologic calcifications, family history of breast cancer and perimenopausal age (37).

Fine needle aspiration biopsy is increasingly popular and quite good for distinguishing between malignant and benign breast disease but is less reliable in predicting which benign breast lesions may become malignant. It has recently been found that image cytometry provides a better means of identifying premalignant lesions of the breast than conventional microscopic examination of the fine needle biopsy specimen (133).

Dietary fat may influence the initiation and promotion of breast tumors through several mechanisms, including the endocrine system. The effects of diet on estrogen metabolism are especially interesting because of the possible role of endogenous estrogen in human breast cancer. The importance of endogenous estrogen for breast cancer is demonstrated by the estrogen dependence of many human breast tumors, the effectiveness of anti-estrogen therapy in treating the disease, the positive association between breast cancer incidence and early menarche, late menopause, late first pregnancy and nulliparity, and the influence of early oophorectomy on lowering breast cancer incidence. Significant and reproducible effects of dietary manipulations on hormone levels was observed in the serum concentrations of estrone sulfate in healthy premenopausal women fed defined diets in a metabolic ward. During an initial 4 week period, all women consumed a typical western diet (40% of total calories from fat, polyunsaturated fat to saturated fat (P:S) ratio of 0.5, cholesterol 400 mg/day and dietary fiber 12 g/day). After this control period, they were switched to a low fat, high fiber diet (25% of total calories from fat, P:S ratio 1.0, cholesterol 200 mg/day, and dietary fiber 40 g/day) for 8-10 weeks. An average decrease of 36% in serum estrone sulfate was observed in women fed the experimental diet (52).

The metabolism of other dietary constituents is also interesting for cancer etiology. Women with galactosemia experience early ovarian failure. The combination of ovarian failure and high levels of pituitary hormones which stimulate the ovary beyond its capacity to respond may combine to increase risk of ovarian cancer. A team of investigators in Boston recently found that consumption of lactose-rich foods, the dietary source of galactose, increased the risk of ovarian cancer. They also observed that the activity of the enzyme, galactose transferase, involved in the conversion of galactose to glucose, was significantly lower in ovarian cancer cases than in controls (30).

Another case-control study found that physician-diagnosed infertility or unsuccessful attempts to conceive had no influence on subsequent ovarian cancer risk, while long periods of unprotected intercourse and a low pregnancy rate enhanced risk. It was hypothesized that an endocrine or physiological disorder associated with ovulation that reduces the likelihood of conception may play a role in epithelial ovarian cancer. This is consistent with many of the epidemiologic features of the disease, namely, the increased risk associated with low fecundity, the less rapid increase of age-specific incidence rates after the menopause and the protective effects of pregnancy and oral contraceptive use (which suppresses ovulation). An analysis of data from two other case-control studies found that the protection afforded by oral contraceptive use was independent of parity and it increased with increasing duration of use (196).

The relationship between nutrition, hormone levels and cancer risk is not always as obvious or easily detected as that reported above. In Washington County, Maryland, serum collected in 1974 was analyzed for levels of androgens and vitamins for men who subsequently developed prostate cancer, and the levels were compared to those for men who did not develop this cancer. On the average, the levels of androgens were slightly higher among the men who developed cancer. Average levels of retinol, beta-carotene, lycopene (a cancer-inhibiting substance found in red fruits), and vitamin E showed only trivial differences between the men who later developed cancer and those who did not. However, interactions were observed between the levels of testosterone and those of both retinol and lycopene. At high vitamin levels, high levels of testosterone had little influence on prostate cancer risk, but at low vitamin levels, risk associated with high levels of testosterone was increased 6-8 times. The degree of interaction remained essentially unchanged after adjustment for the effect of cigarette smoking and education (26).

Another indicator of nutritional status, body mass index, has been associated with prostate cancer risk. Mortality data from prospective studies of Seventh Day Adventists and volunteers from the American Cancer Society in the United States consistently show an enhanced risk of prostatic cancer in overweight men. Investigators in Hawaii recently reported from studies of a cohort of men of Japanese ancestry that risk of prostatic cancer increased as the area of muscle in the arm increased. They did not find any association between the area of fat in the arm and prostate cancer, indicating that lean tissue rather than body fat may play a role in the development of prostatic cancer (121). Since testosterone is an anabolic steroid, these findings are consistent with other investigators' findings of increased levels of testosterone in men at risk of prostatic cancer. Together with a preliminary finding of higher testosterone levels in black than white men, both without known prostate cancer, and the report last year that black men with prostate cancer had higher levels of testosterone than those without cancer, a possible biologic basis for the higher risk of prostatic cancer among black men is suggested.

Data from a population-based case-control study of the association between dietary lipids and lung cancer risk in the multi-ethnic population of Hawaii were recently published. There was a significant positive association with dietary cholesterol and the risk of lung cancer in men, but not in women. The odds ratio for the highest versus the lowest quartile of cholesterol intake was 2.2. The association of cholesterol and lung cancer was consistent for three or four ethnic groups analyzed separately. The effect of cholesterol on the development

of lung cancer was restricted to current cigarette smokers who smoked heavily and to squamous and small cell histologic types of lung cancer. Similar results were found for dietary fat, but because of the high correlation between fat and cholesterol, it was not possible to separate the effects of these nutrients (83).

It was recently reported that previous lung disease and family history of lung diseases are additional risks factors for adenocarcinoma of the lung in women. A history of previous lung disease of any kind was associated with a 40% increase in risk, with a more marked increase in risk for lung diseases during childhood. Previous tuberculosis, exposure to tuberculosis without clinical disease, and family history of lung cancer were each associated with a significant increased risk. Increasing trend in risk was also observed for decreasing intake of dietary beta-carotene (150).

Studies of cancer sites in which cigarette smoking, coffee and alcohol consumption are of interest are difficult to interpret when carried out in populations in which exposure to these substances not only occurs frequently, but exposure to more than one of them is the rule rather than an exception. Studies of religous groups proscribing the use of these substances, including Utah with its high proportion of Mormons, can be helpful in determining the risks associated with these exposures, as demonstrated by subsequent reports.

Pancreatic cancer is one of the most rapidly fatal human malignancies. Cigarette smoking has been found to increase risk of pancreatic cancer in most epidemiological studies. A few years ago an association between coffee consumption and pancreatic cancer independent of cigarette smoking was reported. This observation prompted other studies in which inconclusive results were obtained, some showing a weak effect and others reporting no effect. An advantage of a case-control study recently carried out in Utah is that only about 17% of the adult males are regular cigarette smokers compared to 30% nationally, and 40% drink coffee regularly compared to 85% nationally. Cigarette smoking was found to be an independent risk factor for pancreatic cancer, with odds ratio in the heaviest smoking group of 3.08. Adjustment for age and lifetime coffee consumption reduced the odds ratio to 2.03. There was an increasing risk with increasing number of cups of coffee consumed, with a highly significant test for trend ($p<0.000$). This association was present after adjustment for age, sex and cigarette smoking, but with a lower slope. The increased risk was present for users of regular and decaffeinated coffee, but was stronger in those using decaffeinated coffee, implicating the role of as yet unidentified compounds present in coffee beans in the etiology of pancreatic cancer (113).

In recent years, some epidemiological studies have indicated an association between passive smoking and an increased risk of lung cancer. These studies require careful consideration since investigators in California found that dietary intake of carotene but not of retinol was significantly lower in non-smokers with passive smoking at home than in non-smokers without passive smoking at home. It was concluded that dietary carotene is a potential confounder in studies of the relationship of passive smoking to lung cancer. The estimated relative risk of lung cancer for passive smoking was 2.0, but was lowered to 1.8 if carotene intake was taken into account (45).

Risk associated with passive smoking and squamous cell carcinomas of sites other than lung was investigated by a population-based case-control study of

white females aged 20 to 59 residing in the urban areas of Utah. The risk of cervical cancer associated with passive smoke exposure for three or more hours per day was 2.96. Risk from passive smoke was greater in women who were nonsmokers than in those who smoked. The study population was ideal because a large majority belongs to the Church of Jesus Christ of Latter Day Saints or Mormons, which proscribes the use of tobacco. This study confirmed other studies in finding that cigarette smoking increased risk of cervical cancer after adjusting for age, educational level, church attendance, and sexual activity. The adjusted risk estimate associated with being a current smoker was 3.42, for smoking 100 or more cigarettes during the lifetime it was 2.21, and for having smoked five or more pack years it was 2.81 (113).

Several studies have noted that adenocarcinomas arising from the gastric cardia share epidemiologic features with adenocarcinomas arising from the esophagus and gastroesophageal junction in distinction from the more common distal gastric tumors. These shared features are: predominance among males, lower mean age at diagnosis, increased frequency of occurrence over time, increased risk associated with alcohol and tobacco use, frequency of concomitant hiatal hernia, and less frequent association with chronic gastritis. Recently, data from the Surveillance, Epidemiology and End Results (SEER) program were analyzed to estimate the incidence of adenocarcinoma of the gastric cardia and distal stomach in the United States. The annual incidence of gastric cardia adenocarcinomas was 1.1 and that for the distal stomach was 3.8 per 100,000 persons. The male to female ratio for adenocarcinoma arising in the cardia was 7.0, but 2.2 for that arising in the distal stomach. This sex ratio shifted across age groups for the gastric cardia and was highest for the 50-59 year old age group, but remained relatively stable across groups for cancers of the distal stomach. Over the decade studied, the sex ratio decreased from 8.0 to 4.6 for gastric cardia tumors, but remained constant for adenocarcinoma of the distal stomach. Blacks were 2.5 times more likely to develop adenocarcinoma of the distal stomach than whites, but had a 50% lower risk of gastric cardia tumors than whites. These results indicate that adenocarcinoma of the gastric cardia, gastroesophageal junction and distal esophagus are etiologically distinct from distal gastric tumors (181).

Projections: Molecular or biochemical cancer epidemiology is a relatively new discipline which attempts to merge laboratory and conventional epidemiological methods in order to better identify causative factors and to detect and assess human cancer risk more precisely. In particular, laboratory techniques can be used to identify and quantitate the amount of activated carcinogen that actually reaches target tissue, thereby overcoming a major limitation of conventional epidemiology, namely, the reliance on estimated exposure based on ambient concentrations of the agent. Approaches are being developed and applied at the cellular level to quantitate biologically effective dose indicators, such as carcinogen-DNA adducts, and preclinical response indicators like chromosome alterations. Recent developments in the understanding of oncogenes and their protein products offer new opportunities for the molecular epidemiology of occupational cancer through the use of these markers which seem to be critically involved in the carcinogenic process. Thus, for example, through the application of immunoblotting of urine or serum with monoclonal antibodies to various oncogene proteins in cohorts of workers exposed to potential carcinogens, it may be feasible to identify those individuals at risk for the development of occupational cancer at a sufficiently early stage that the oncogenic process

could be aborted. A number of studies in the area of biochemical epidemiology have recently been initiated. The scope of these studies range from use of caffeine metabolite ratio for the determination of human exposure to compounds which induce cytochrome P450; determining the frequency of nuclear DNA lesions, expressed as micronuclei, in lymphocytes obtained from subjects exposed to ionizing radiation; studies of correlation between dietary intake of aflatoxins to levels of excreted aflatoxin B_1-DNA adducts, oxidative metabolites in urine, aflatoxin M_1 in human milk and covalently bound aflatoxin to serum albumin; determination of excreted alkylated purines as markers of DNA alkylation in vivo in humans; to use of carnitine as a biochemical marker of fat intake.

Confirmatory studies of hormonal metabolism in individuals of differing races, as well as studies exploring the interaction of diet and testosterone metabolism, are needed to enhance understanding of prostate cancer etiology. Interest in epidemiologic studies of colorectal adenomas and carcinoma has increased, stimulated perhaps by the exciting finding of a strong genetic predisposition for adenomas reported last year. There has also been a strong interest in better definition of breast cancer risks associated with oral contraceptive usage for long periods prior to first childbirth. This has led to the initiation of a new cohort study of nurses, which is expected not only to provide much better definition for the question relating to oral contraceptives, but to yield important information about other cancer risk factors in women over the next decade or so. It will be conducted in parallel with the older nurse cohort study.

AIDS-RELATED EPIDEMIOLOGY

Description: The AIDS-Related Epidemiology component of the Branch emphasizes the identification of risk factors for the acquired immunodeficiency syndrome (AIDS) and AIDS-associated malignancies (50%), etiologic mechanisms for the development of malignancies with human immunodeficiency virus (HIV) and other retrovirus infection (40%), and clarification of the role of other viruses in AIDS-associated malignancies (10%). The overall objective of the program is to establish the etiology, natural history, and incidence of malignancies and premalignant conditions in HIV-infected individuals. Of particular interest are studies on the effect of HIV variation, infection with related retroviruses and other viruses, immune alteration, and anti-viral treatments on the development and progression of neoplasia. While grants and cooperative agreements provide most of the support for these activities (18,19,41,57,65,78,82,88,97,114,115, 141,152,159), the Branch continues to collaborate with the National Institute of Allergy and Infectious Diseases (NIAID) to support contracts for the study of the natural history of HIV infection in homosexual men (216,227,228).

Research Accomplishments: Investigators supported by this program are attempting to identify the risk factors for HIV and human T-lymphotropic virus type I (HTLV-I) infection and disease progression (41,114,216,227,228). In a prospective study conducted in Miami, the spouses or long-term heterosexual partners of patients in various clinical stages of HIV infection are being followed. Among the spouses (partners) enrolled, there is no difference between men and women in seroprevalence of antibodies to HIV, 26% and 21% respectively. Presence of HIV antibody in a spouse correlates directly with the severity of HIV disease in the index case, the presence of p24 antigen in the index case, a low CD4 cell count in asymptomatic index cases, presence of genital herpes or gonorrhea in the

spouse, and with lack of condom use in the preceding year. The length or frequency of sexual contact and the types of sexual activity do not correlate with the presence of antibody to HIV in a spouse. In this population, the risk for heterosexual acquisition of HIV appears to be relatively equal for men and women in a monogamous relationship, and increase with advancing disease and the development of p24 antigenemia in the index case. In addition, other sexually transmitted diseases or potential breaks in epithelial membranes may play a role in heterosexual transmission of HIV. Children of the index cases have also been enrolled in the prospective study. All children seropositive to HIV were born to mothers with HIV infection; none of the seronegative children have converted during the study period (41).

The program continues to collaborate in the Multicenter AIDS Cohort Study (MACS): 5,000 asymptomatic homosexual men from Baltimore, Chicago, Los Angeles, and Pittsburgh were recruited in the spring of 1984 and are being followed semiannually for the development of AIDS, AIDS-related symptoms, and malignancies (216,227,228). One hypothesis to explain the increased ability to transmit HIV with an increase in severity of HIV-related disease is that HIV isolates from asymptomatic men are less virulent than virus isolates from AIDS patients. The growth of these two types of virus isolates obtained from participants in the MACS was compared in vitro in H9 cells and phytohemagglutinin (PHA)-treated fresh peripheral blood lymphocytes (PBL). Of isolates from asymptomatic men, less than one-fourth could productively infect H9 cells or mitogen-stimulated PBL. In contrast, nearly all HIV isolates from AIDS patients showed productive infection in both H9 cells and PBL (216).

Turning to studies of seroconversion, the latency period between initial infection with HIV and the development of antibodies has recently been an area of active research. The polymerase chain reaction (PCR) technique was used to detect HIV provirus in lymphocytes obtained serially from seroconverters in the MACS cohort. Sera and PBL were studied 18, 12 and 6 months prior to the first positive Western blot and at the time of seroconversion. Results of PCR amplification data showed that all seroconverters were PCR positive at the time of seroconversion, and most were PCR positive 6 to 12 months before the first positive Western blot. Additional seroconverters are being evaluated (227).

HTLV-I is a retrovirus known to cause adult T-cell leukemia/lymphoma and spastic paraparesis. In a study of HTLV-I transmission and natural history, a Japanese population in a region of high HTLV-I prevalence has been surveyed by interview and serology. Two potential pre-clinical markers of HTLV-I infection outcome have been identified: the presence of circulating atypical lymphocytes with a characteristic convoluted nuclear configuration, and reduced response to purified protein derivative (PPD) of tuberculin. Atypical lymphocytes are thought to represent HTLV-I-infected T-cells. Atypical lymphocytes were more prevalent among persons who were likely to have been infected perinatally rather than sexually with HTLV-I. It may be that adult T-cell lymphoma is related to perinatal infection with the presence of atypical lymphocytes marking an intermediate stage in the progression to lymphoma. There was a significantly inverse association between the degree of PPD response and prevalence of HTLV-I antibody, which was much stronger among subjects aged 60 years or older than among younger persons. These findings indicated that there is sub-clinical immunosuppression among HTLV-I carriers, which increases with age. Also, the concordance of HTLV-I-antibody was evaluated in married couples in the Japanese

cohort. There was a predominance of female seropositivity among the discordant couples, suggesting that men are more likely to infect women than women are to infect men (114).

In studies of HIV-associated malignancies, suggestive associations have previously been reported between Kaposi's sarcoma (KS), presence of the DR-5 antigen of the human leukocyte antigen (HLA) system, and immunosuppression. The data regarding the association of KS, nitrite use, cytomegalovirus (CMV) antibodies, and integrated viruses (CMV, HIV, hepatitis B virus, human herpesvirus 6, or EBV) have been inconsistent. A case-control study of homosexual men with KS was conducted in New York City to investigate risk factors associated with KS. Among the factors studied were drug and sexual practices, disease histories, exposures to chemicals, viruses and other infectious agents, possible genetic predispositions including HLA type, and immunologic abnormalities. KS cases did not differ significantly from seropositive homosexual controls in age, race, education, or residence. CMV exposure was similar among cases and controls, as assessed by presence of anti-CMV IgG and IgM. Reported usage of amyl, butyl, unlabelled or total nitrites was not different between cases and controls. Analyses of the numbers of different sexual partners and of various sexual activities revealed that KS cases were less sexually active than seropositive controls. Additional analyses are currently underway.

Recent analyses of temporal trends in KS incidence have shown a decline in KS as a proportion of initial AIDS diagnoses, and no change over time in the proportion of AIDS patients ever developing KS. Incidence of KS and non-KS AIDS was observed in the MACS. The incidence of KS was approximately constant over time in this carefully studied cohort, even when KS was analyzed as a proportion of initial AIDS diagnoses. Initial analysis of risk factors for KS in the MACS suggested that KS cases tended to engage in more frequent rimming (suggesting oral-genital transmission) for two years prior to the KS diagnosis. Drug use, frequency of sexually transmitted diseases, age at first sexual activity, and educational level were not associated with the development of KS. Additional analyses will focus on antibody titers to CMV and other viruses (227).

Projections: The Branch continues to encourage new investigations of the incidence and etiology of malignancies associated with HIV infection. The Request for Applications (RFA) on epidemiologic studies of HIV-associated malignancies was reissued in 1988. Two to four new studies submitted in response to the RFA may be funded this year. It is anticipated that these studies will provide additional information on the incidence, distribution and mechanisms of development of these retrovirus-associated cancers. A meeting of grant recipients working on the epidemiology of HIV-associated malignancies is planned for the fall of this year.

SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM

Description: The Small Business Innovation Research (SBIR) Program, now in its sixth year at NIH (fourth year for the contract mechanism), is just now reaching maturity as a responsive research program. No longer must funding components reach down to generally unfundable scores to exhaust mandated funds. Scores are competitive with traditional programs, but submissions are generally sparce by comparison. Several contracts and grants have reached phase II

completion and are in the process of seeking venture capital support. Established by the Small Business Innovation Development Act of 1982 and legislatively extended through FY93, this program mandates a 1.25% set-aside for every Federal agency with a research and development budget in excess of $10 million to encourage small business participation, especially disadvantaged and minority-owned, in Federal research and subsequent translation into a commercially marketable product. SBIR grants are accepted three times a year, while contracts are solicited only once a year. Both undergo peer review and pass through two phases of research: a feasibility study limited to six months at no more than $50,000 total cost followed by an in-depth developmental effort of up to two years and $500,000 total cost. Those projects moving on to phase III must generally find funding outside the Federal government. In FY 89 the National Cancer Institute spent $20 million on SBIR. As in the previous fiscal year, the majority of ongoing projects, all six grants and eight of 15 contracts, were software-related. The SBIR program lends itself well to software development, especially in the fields of epidemiology and biostatistics.

Research Accomplishments: Of the six SBIR grants active during FY89, one phase I and one phase II are terminating. The former project (79) has been dealing with the development of prototype software for the detection of changes in cancer incidence and mortality in defined geographical areas based on registry information. Comparisons of these data with environmental data from other sources can also be accomplished. The latter study (102) has extended exact analysis techniques for categorical data from unstratified to stratified populations and from two-sample to multi-sample problems. Furthermore, this code is being implemented by addition to mainframe (SAS) and microcomputer (SYSTAT and EGRET) statistical packages. A stand-alone module is also under development. The remaining four SBIR grants are newly awarded and deal with widely varying implementations of microcomputer software. One project (132) will create a Dietary Constituent--Cancer Modulation Analysis System for assessing relationships between cancer and dietary factors (trace elements, food additives, contaminants, and food consumption data) in the population. Another effort (24) will develop a user-friendly microcomputer interface through the SYSTAT software package to make use of the powerful yet complex mainframe-oriented Continuous Time Program for modelling studies. A third study (128) will convert CLAB, a series of cluster analysis algorithms embedded in the modelling package MLAB, into software suitable for use in the microcomputer environment. This effort will be extended to customize CLAB for flow cytometric diagnosis of AIDS and leukemia. The final project (161) will provide the Directory of Ongoing Research in Cancer Epidemiology on CD-ROM for use with personal computers. It will be used in conjunction with existing modified search software to make this extensive resource more easily accessible.

There were 15 SBIR contracts active during FY89, four phase II and 11 new phase I studies. Of the three terminating phase II efforts, two were software projects and one was concerned with pesticide detection. The first computer effort (213) involved the creation of a bibliographic software package capable of transforming R:Base, DBase, or user-supplied references into citations following the guidelines of any of several popular biomedical journals. Both input and output formats can be specified by the user or default to a format provided by the package. The other terminating software contract (225) is a truly successful SBIR project. This sophisticated microcomputer package for epidemiologists, known as EGRET, helps analyze the statistical soundness of data from field and

clinical studies. It will also provide assistance in the careful planning of future studies. Having undergone extensive worldwide beta testing and use in West Coast graduate level courses, this package has sold nearly 100 pre-release copies ($495/each). The final terminating contract (223) describes the use of supercritical fluid chromatography to detect the presence and burden level of various hard-to-analyze pesticides and their metabolites in mammalian systems. The only remaining ongoing phase II contract (219) concerns the preparation of highly specific monoclonal antibodies to DNA adducts of acrolein. Ultimately, this study should result in immunologic assay kits to detect/monitor exposure to such agents in the workplace. The newly-awarded phase I SBIR contracts cover a wide array of topics: five (210,212,214,224,226) are developing statistical software for the generation of probability curves and tables as well as their confidence limits on the microcomputer from the underlying algorithms; two (217,222) will devise a durable bar coding and tracking system for NCI repository specimens to maintain inventory and document investigator requests; one (215) will validate the use of the already existing C-Probe indicator as a personal chemical carcinogen exposure monitor; one (218) will synthesize gene coding sequences for the various portions of the HTLV-1 envelope protein in preparation of assay reagents for human serum screening; one (211) will provide a software system for manipulating NCI mortality data on CD-ROM for the research community; and one (220) is designing a regional cancer registry coordination center capable of accessing and reformatting available registry data as a resource to epidemiologists.

Projections: Based on the President's Budget, NCI will spend another $20 million on SBIR projects in FY90. Although the number of SBIR grant applications is slowly increasing and their review survival is improving, their overall impact remains almost non-existent since the conversion rate from phase I to phase II is under 10% even with three receipt dates during the year. Contracts, on the other hand, although received only once a year, fare somewhat better in review and conversion to phase II funding (33%). Recently PHS has issued a position paper on the SBIR program in favor of increasing the phase I limits to one year and $75,000 total cost with early submission of the phase II application. Furthermore, phase II submissions could be made without having performed the phase I if the participant had already carried out the feasibility study privately. In addition, Congress is considering the possibility of making the SBIR program a permanent line item in the budget and increasing the set-aside to 3-5% of the R&D total. These changes would make the program much more attractive to small businesses and would probably result in a significant increase in participation. The Extramural Programs Branch, in collaboration with the intramural scientists of the Epidemiology and Biostatistics Program, are presenting five topics for inclusion in the Omnibus SBIR Contract Solicitation in FY 90. Three of the five topics are aimed at distinguishing HTLV-1 from HTLV-2, while the remaining two are concerned with developing genetic probes for malignant melanoma and debrisoquine metabolism. It is likely that these five new topics will result in six to eight phase I proposals, four of which will probably be awarded in FY90. Furthermore, four of the 11 new phase I contracts should convert to phase II efforts within that time frame. The slightly increased success with SBIR grant applications in FY 89 indicates the possibility of ten or more responses leading to four phase I awards. These, in addition to the recent phase I awards this year, could result in two or three phase II conversions in FY 90. This Branch remains committed to the ideals of the SBIR program and welcomes any chance to further its goals.

EXTRAMURAL PROGRAMS BRANCH

GRANTS ACTIVE DURING FY 89

	Investigator/Institution/Grant Number	Title
1.	ANDERSON, David E. Univ. of Texas Sytem Cancer Ctr. 5 R01 CA 29614-07	Genetics of Breast Cancer
2.	ANDERSON, David E. Univ. of Texas System Cancer Ctr. 5 R01 CA 40173-04	Genetic Epidemiology of Male and Female Breast Cancer
3.	ANDERSON, Harold D. Stephens College 1 R15 CA 41999-01A2	Trace-Element Nutrition & Cancer Etiology
4.	AUSTIN, Harland D. University of Alabama, Birmingham 5 R01 CA 39733-04	Case-Control Study of Endometrial Cancer & Obesity
5.	AWERBACH, Tamara E. Harvard University 5 R01 CA 37820-05	Mathematics of Diffusion Assays--Mutagens & Antibiotics
6.	BARTSCH, Helmut Int'l Agency Res. Cancer 5 U01 CA 43176-03	DNA Damage as a Marker of Exposure to Betel Quid/Tobacco
7.	BECKER, Thomas M. University of New Mexico 1 R29 CA 48003-01	Epidemiology of Cervical Dysplasia in Minority Women
8.	BECKMANN, Anna M. Fred Hutchinson Cancer Res. Ctr. 1 R03 CA 50491-01	Detection of HPV with the Polymerase Chain Reaction
9.	BEGG, Colin B. Dana-Farber Cancer Institute 5 R01 CA 35291-06	Treatment Allocation in Sequential Clinical Trials
10.	BEGG-MARINO, Lisa University of Pittsburgh 5 R01 CA 44751-02	Epidemiology of Obesity, Sex Hormones & Breast Cancer
11.	BERESFORD, Shirley A. University of Washington 1 R01 CA 47749-01A1	Endometrial Cancer Risk and Post-Menopausal Hormone Use

12.	BERKOWITZ, Gertrud S. Mt. Sinai Sch. Med. 5 R29 CA 47053-03	Prevalence & Epidemiology of Cryptorchidism
13.	BERNSTEIN, Leslie University of Southern California 5 R01 CA 44546-03	A Case-Control Study of Breast Cancer in Young Women
14.	BISHOP, David T. University of Utah 5 R01 CA 36362-06	Linkage Analysis & Multiple Loci
15.	BOYD, Norman F. Ontario Cancer Institute 1 R01 CA 48997-01A1	Plasma Lipids and Familial Breast Cancer
16.	BRADLOW, H. Leon Rockefeller University 5 R01 CA 39734-05	Obesity, Diet, Estrogens & Cancer Risk
17.	BRESLOW, Norman E. University of Washington 5 R01 CA 40644-05	Statistical Methods in Cancer Epidemiology
18.	BROOKMEYER, Ronald S. Johns Hopkins University 5 R01 CA 48723-02	Development & Application of Statistical & Quantitative Methods in AIDS Research
19.	BUCKLEY, Jonathan D. University of Southern California 2 R01 CA 38908-04	Epidemiology/Biology of Childhood Non-Hodgkin's Lymphoma
20.	BUFFLER, Patricia A. University of Texas Hlth. Sci. Ctr. 2 R01 CA 34448-04	Occupational & Environmental Exposures in the Etiology of Adult Leukemia
21.	BURT, Randall W. University of Utah 2 R01 CA 40641-04	Inheritance of Discrete Colorectal Adematous Polyps
22.	CAMPBELL, T. Colin Cornell University, Ithaca 5 P01 CA 33638-06	Diet & Cancer in China
23.	COLDITZ, Graham Brigham & Women's Hospital 5 R01 CA 46475-03	Benign Breast Disease & Risk of Breast Cancer
24.	COLLA, Phillip L. Salford Systems 1 R43 CA 48554-01A1	Systat Interface for the Continuous Time (CTM) Program

25. COLTON, Theodore
Boston University
5 R01 CA 40240-05

Breast Cancer Risk in Women Given DES in Pregnancy

26. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 36390-05

Serologic Precursors of Cancer

27. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 47503-02

Blood & Data Bank for Cancer Risk Factor Studies

28. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
5 P01 CA 28842-08

Etiologic Studies of Gastric Carcinoma

29. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
2 R01 CA 40095-04

Lung Cancer in Non-Smoking Women

30. CRAMER, David W.
Brigham & Women's Hospital
5 R01 CA 42008-03

Correlates of Ovarian Cancer Risks

31. DALING, Janet R.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 35881-06

Vulvar Cancer--Epidemiology, Biochemistry & Immunology

32. DALING, Janet R.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 41410-04

Epidemiology of Penile & Urethral Cancer

33. DALING, Janet R.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 41416-04

Breast Cancer in Relation to Prior Induced Abortion

34. DAVIS, Scott
Fred Hutchinson Cancer Res. Ctr.
5 R03 CA 45684-02

Nutritional Factors & Cancer of the Pancreas

35. DAVIS, Scott
Fred Hutchinson Cancer Res. Ctr.
5 R03 CA 48907-02

Nutritional Factors & Non-Hodgkin's Lymphoma

36. DE METS, David L.
University of Wisconsin, Madison
5 R01 CA 18332-15

Statistical Problems in Cancer Research

37. DUPONT, William D.
Vanderbilt University
5 R01 CA 46492-02

Breast Cancer in Women with Proliferative Breast Disease

38. ELSTON, Robert C.
Louisiana State Univ. Med. Ctr.
5 R01 CA 28198-10
Statistical Genetic Analysis for Cancer Families

39. FILIPOVICH, A. H.
University of Minnesota
5 U01 CA 44120-02
Extramural Utilization of the Immunodeficiency Cancer Registry

40. FINKELSTEIN, Dianne M.
Massachusetts General Hospital
5 R01 CA 47048-03
Carcinogenicity Experiments for Environmental Health

41. FISCHL, Margaret A.
University of Miami
5 R37 CA 34988-07
Heterosexual & Household Transmission of HTLV-III

42. FOLSOM, Aaron R.
University of Minnesota
5 R01 CA 39742-05
Distribution of Body Fat & Cancer Risk in Women

43. FRASER, Gary
Loma Linda University
5 R01 CA 14703-14
Cancer Epidemiology in Adventists - a Low Risk Group

44. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R37 CA 19939-13
Drug Surveillance: Cancer & Other Adverse Effects

45. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R01 CA 36074-05
Are Low-Yield Cigarettes Less Hazardous?

46. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
1 R35 CA 49761-01
Cancer Epidemiology in a Large Health Care Plan

47. GELLER, Nancy L.
Sloan-Kettering Institute
5 R01 CA 43074-03
Statistical Methods for Cancer Clinical Trials

48. GERMAN, James L.
New York Blood Center
5 R01 CA 38036-05
Maintenance of the Bloom's Syndrome Registry

49. GIESE, Roger W.
Northeastern University
5 R01 CA 35843-06
Ultratrace Analysis of DNA Lesions with Electrophoresis

50. GIESE, Roger W.
Northeastern University
5 U01 CA 43012-03
Chemical Digestion--GC/MS Analysis of DNA Adducts

51.	GOLD, Ellen B. University of California 1 R01 CA 50371-01	Family History in Children with Brain Tumors
52.	GORBACH, Sherwoood L. Tufts University 5 R37 CA 45128-04	Diet, Estrogens, & Breast Cancer
53.	GRAHAM, Saxon State University of New York, Buffalo 5 P01 CA 11535-18	Social Epidemiology of Cancer
54.	GROOPMAN, John D. Boston University 5 U01 CA 49409-02	Monitoring Human Exposure to Aflatoxins in the Gambia
55.	GRUFFERMAN, Seymour University of Pittsburgh 5 R01 CA 21244-08	The Epidemiology of Childhood Rhabdomyosarcoma
56.	GRUFFERMAN, Seymour University of Pittsburgh 5 R01 CA 47473-03	Case-Control Study of Hodgkin's Disease in Childhood
57.	GRUFFERMAN, Seymour University of Pittsburgh 5 R01 CA 48643-02	Epidemiologic Studies of HIV-Associated Malignancies
58.	HAILE, Robert W. Univ. of California, Los Angeles 5 R01 CA 36387-06	Genetic-Epidemiologic Study of Bilateral Breast Cancer
59.	HANASH, Samir M. University of Michigan, Ann Arbor 5 P01 CA 26803-09	Program Project: The Study of Human Mutation
60.	HARRINGTON, David P. Dana-Farber Cancer Institute 5 R01 CA 39929-05	Nonparametric Statistical Tests for Censored Cancer Data
61.	HENDERSON, Brian E. University of Southern California 1 R13 CA 49520-01A1	Sixth Symposium on Epidemiology & Cancer Registries/Pacific Basin
62.	HERBST, Arthur L. University of Chicago 5 R01 CA 42250-03	Breast Cancer & Other Health Risks in DES Mothers
63.	HOFFMANN, Dietrich American Health Foundation 5 R01 CA 40070-03	Biochemical Validation of Smoke Absorption by Infants

64. HOLFORD, Theodore R.
Yale University
2 R01 CA 30931-08A1
Systematic Analysis: Connecticut Cancer Incidence Trends

65. HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 42440-03
Mutagenic Mucus in the Uterine Cervix of Smokers

66. HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 45614-02
Epidemiology of Non-Hodgkin's Lymphoma & Retroviral Tests

67. HOLMES, King K.
University of Washington
5 R01 CA 34493-06
Etiology & Natural History of Cervical Neoplasia

68. HSIEH, Chung-Cheng
Harvard School of Public Health
1 R01 CA 44683-01A1
Case-Control Study of Cancer of Extrahepatic Bile Duct

69. HSU, Jason C.
Ohio State University
2 R01 CA 41168-03
Multiple Comparisons with the Best Treatment

70. HULKA, Barbara S.
University of North Carolina
5 R03 CA 46437-02
The Role of Human Papillomavirus in Cervical Neoplasia

71. HULKA, Barbara S.
University of North Carolina
1 R03 CA 47076-01
Lipid Changes & the Incidence of Cancer

72. HUTCHISON, George B.
Harvard University
5 R01 CA 38071-04
Epidemiology of Non-Hodgkin's Lymphoma

73. JANGHORBANI, Morteza
University of Chicago
5 R01 CA 38943-05
Assessment of Selenium Status in Man

74. JENSON, Ronald H.
Univ. of California, Livermore
5 U01 CA 48518-02
Glycophorin A-based Assay of Somatic Cell Mutations

75. KAKAR, Faiz
Fred Hutchinson Cancer Res. Ctr.
1 U01 CA 48370-01
Carnitine as a Biochemical Marker of Fat Intake

76. KALOW, Werner
University of Toronto
5 U01 CA 48354-02
Caffeine Metabolic Ratios Serving Epidemiology

77. KAMPERT, James B.
Stanford University
5 R23 CA 41477-03
Modified Score Methods for Cancer Case-Control Studies

78. KATZ, Ben Z.
Yale University
5 R01 CA 48270-02
EBV-Associated Lympho-proliferations in AIDS

79. KENNEDY, Susan
Poolman, Shih & Platton, Inc.
1 R43 CA 47688-01
Cancer Management Mapping System

80. KING, Mary C.
Univ. of California, Berkeley
5 R01 CA 27632-10
Genetic Epidemiology

81. KIRSCHNER, Marvin A.
Newark Beth Israel Med. Ctr.
5 R01 CA 39767-03
Androgen & Estrogen Dynamics in Obesity

82. KIVIAT, Nancy
Harborview Medical Center
1 R01 CA 50738-01
Epidemiology of Anal Dysplasia in HIV Positive & Negative Men

83. KOLONEL, Laurence N.
University of Hawaii, Manoa
5 P01 CA 33619-07
Epidemiologic Studies of Diet & Cancer in Hawaii

84. KOZIOL, James A.
Scripps Clinic & Res. Fdn.
5 R01 CA 41582-04
Topics in Biostatistics

85. LAGAKOS, Stephen W.
Harvard University
5 R01 CA 33041-08
Biostatistical Methods for Carcinogenicity Experiments

86. LAGAKOS, Stephen W.
Dana-Farber Cancer Institute
5 R01 CA 39640-05
Biostatistical Problems in Cancer Research

87. LE MARCHAND, Loic
University of Hawaii, Manoa
5 R29 CA 44503-03
Body Weight in Youth & Middle Age as Predictors of Cancer

88. LEVINE, Alexandra M.
University of Southern California
1 R01 CA 50850-01
Epidemiology of HIV-Related Lymphoma

89. LEY, Ronald D.
Lovelace Medical Foundation
5 U01 CA 48391-02
Stratospheric Ozone Depletion & Increased DNA Damage

90. LIVINGSTON, Gordon K.
University of Cincinnati
5 U01 CA 48429-02
Micronuclei (DNA Lesions) as Markers of Human Exposure

91. LONDON, W. Thomas
Fox Chase Cancer Center
2 P01 CA 40737-04A1
Hepatitis B Virus & Primary Hepatocellular Carcinoma

92. LUSTBADER, Edward D.
Fox Chase Cancer Center
5 R01 CA 43077-02
Epidemiology of Familial Aggregation Colo-Rectal Cancer

93. LYNCH, Henry T.
Creighton University
5 R01 CA 41371-03
Hereditary Nonpolyposis Colorectal Cancer Resource

94. LYNCH, Henry T.
Creighton University
5 R01 CA 47429-02
Gene Probes in the FAMMM

95. MACK, Thomas M.
University of Southern California
5 R35 CA 42581-04
Epidemiologic Research in Cancer Etiology

96. MACMAHON, Brain
Harvard University
5 R01 CA 47305-02
Alcohol Consumption, Lactation, & Breast Cancer Risk

97. MAKUCH, Robert W.
Yale University
1 R03 CA 50287-01
Analysis of Repeated T4 Data to Predict KS Risk

98. MC DOUGALL, James K.
Fred Hutchinson Cancer Res. Ctr.
5 P01 CA 42792-03
HPV: Biology, Clinical Significance, & Epidemiology

99. MCGLYNN, Katherine A.
Fox Chase Cancer Center
1 R03 CA 48798-01
Smoking, Hepatitis B Viral Replication and Liver Damage

100. MEADOWS, Anna
Children's Hospital, Philadelphia
5 R01 CA 29275-07
The Epidemiology of Childhood Brain Tumors

101. MEHTA, Cyrus R.
Dana-Farber Cancer Institute
5 R01 CA 33019-08
Statistical Methods for Cancer Treatment & Prevention

102. MEHTA, Cyrus R.
Cytel Software Corporation
5 R44 CA 36681-03
Software for Exact Analysis of Categorical Data

103.	MELAMED, Myron R. Memorial Hosp. for Cancer & Allied Dis. 5 R01 CA 42830-03	Mathematical Model to Evaluate Lung Cancer Screening
104.	MELTON, L. Joseph Mayo Foundation 5 R01 CA 46332-03	Breast Cancer Risk Assessment in Benign Breast Disease
105.	MENCK, Herman R. University of Southern California 5 R01 CA 35477-05	Case-Control Study of Gall Bladder Cancer
106.	MILLER, Kenneth J. Rensselaer Polytechnic Inst. 5 R01 CA 28924-06	Computer Assisted Analysis of Carcinogenicity
107.	MIRVISH, Sidney S. Univ. of Nebraska Med. Ctr. 5 U01 CA 43236-03	Establishing the Basis of the Nitrosoproline Test
108.	MODAN, Baruch Chaim Sheba Medial Center 5 R01 CA 45253-02	Neonatal Phototherapy & Childhood Malignancy
109.	MONSON, Richard R. Harvard University 5 R01 CA 22849-12	Second Cancers in Patients with Hodgkin's Disease
110.	MOOLGAVKAR, Suresh H. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 47658-02	Biomathematical Approaches to Cancer
111.	MORRISON, Alan S. Brown University 5 R01 CA 38707-03	Relation of Benign Hyperplasia to Carcinoma of Prostate
112.	MORRISON, Alan S. Brown University 5 R01 CA 42267-03	Rectosigmoid Polyps & Risk of Colorectal Cancer
113.	MOSER, Royce University of Utah 5 P01 CA 34243-05	Epidemiologic & Biochemical Studies of Nutrition
114.	MUELLER, Nancy E. Harvard University 2 R01 CA 38450-04A1	Risk Factors for Human T-Cell Leukemia Virus Infection
115.	MUELLER, Nancy E. Harvard University 5 R01 CA 44578-02	The Epidemiology of "Classic" Kaposi's Sarcoma

116.	NAGAMANI, Manubai University of Texas Med. Br. 5 R01 CA 45181-02	Ovarian Steroids in Menopausal Women with Endometrial Cancer
117.	NEUGUT, Alfred I. Columbia University 5 R01 CA 37196-03	A Case-Control Study of Colorectal Polyps
118.	NEUGUT, Alfred I. Columbia University 1 R03 CA 51186-01	Pilot Study for Tel Aviv Randomized Sigmoidoscopy Trial
119.	NEWCOMB, Polly Ann Univ. of Wisconsin Clin. Cancer Ctr. 5 R01 CA 47147-02	Alcohol Consumption, Lactation, & Breast Cancer Risk
120.	NIERENBERG, David W. Dartmouth Medical School 5 R03 CA 46412-02	Seasonal & Diurnal Variation in Serum Carotenoids
121.	NOMURA, Abraham M. Kuakini Medical Center 5 R01 CA 33644-07	Cancer Epidemiology of the Migrant Japanese in Hawaii
122.	O'NEILL, Ian K. Int'l Agency Res. Cancer 5 R01 CA 39417-04	In Vivo Microcapsule Monitoring of Carcinogens
123.	OLSHEN, Richard A. University of California, San Diego 5 R01 CA 41628-05	Biostatistics: Modeling & Inference
124.	PAFFENBARGER, Ralph S. Stanford University 5 R01 CA 44854-02	Physical Activity, Body Size, & Cancer Incidence
125.	PAGANINI-HILL, Annlia University of Southern California 2 R01 CA 32197-08	Estrogens & Vitamin A Role in Disease Prevention
126.	PAGANO, Marcello Harvard University 5 R01 CA 42982-02	Algorithms for Analyzing Discrete Data
127.	PASTERNACK, Bernard S. New York University 5 R01 CA 34588-05	Endocrine & Environmental Factors in Breast Cancer Human Subjects
128.	PEARSON, Glenn F. Civilized Software, Inc. 1 R43 CA 50794-01	Addition of Cluster Analysis Capabilities to PC-MLAB

129. PERERA, Frederica P.
Columbia University
5 U01 CA 43013-03
Biological Markers of Ethylene Oxide & Styrene Exposure

130. PERZIN, Karl H.
Columbia University
5 R01 CA 46470-03
Risk of Breast Cancer After Proliferative Benign Disease

131. PETERS, Ruth K.
University of Southern California
5 R01 CA 44401-03
Case-Control Study of Adenocarcinoma of the Cervix

132. PETERSEN, Barbara J.
Technical Assessment Systems, Inc.
1 R43 CA 50045-01
Dietary Constituent Cancer Modulation Analysis System

133. PETRAKIS, Nicholas
Univ. of California, San Francisco
5 P01 CA 13556-17
Epidemiology & Natural History of Breast Cancer

134. PETRAKIS, Nicholas
Univ. of California, San Francisco
5 R01 CA 47288-02
Breast Cancer Incidence in Women with Abnormal Breast Cytology

135. PETREK, Jeanne A.
Memorial Hosp. for Cancer & Allied Dis.
5 R01 CA 47172-02
Adipose Fatty Acid Composition & Breast Cancer Risk

136. PIERCE, Donald A.
Oregon State University
5 R01 CA 27532-06
Statistical Methodology for Response-Time Data

137. PIKE, Malcolm C.
University of Southern California
1 R01 CA 48774-01A1
A Case-Control Study of Post-Menopausal Endometrial Cancer

138. PIKE, Malcolm C.
University of Southern California
1 R03 CA 49432-01
Hormones & Smoking - Endometrial Cancer Relationship

139. PRESTON-MARTIN, Susan
University of Southern California
5 R01 CA 47082-02
Childhood Brain Tumors & N-Nitroso Exposures: U.S. Studies

140. QIAN, Geng-Sun
Shanghai Cancer Institute
5 R03 CA 47128-02
Aflatoxin Contamination of Commonly Eaten Foods

141. RAGNI, Margaret V.
University of Pittsburgh
1 R01 CA 50849-01
Study of HIV-Associated Malignancy in Hemophiliacs

142. RANDERATH, Kurt
Baylor College of Medicine
5 U01 CA 43263-04
Detection & Measurement of Human DNA Adducts

143. ROBISON, Leslie L.
Univ. of Minnesota, Mnpls.-St.Paul
5 R01 CA 42479-03
Epidemiologic Study of Acute Leukemia in Infants

144. ROBISON, Leslie L.
Univ. of Minnesota, Mnpls-St.Paul
5 R01 CA 48051-02
Epidemiology of Childhood Acute Lymphoblastic Leukemia

145. ROBISON, Leslie L.
Univ. of Minnesota, Mnpls-St.Paul
1 R01 CA 49450-01
Acute Nonlymphoblastic Leukemia in Children

146. RODDY, Ronald E.
Family Health International
1 R01 CA 50375-01
A Study of Liver Cancer and the Use of Contraceptives

147. RODRIGUEZ, Carlos C.
State University of New York, Albany
5 R01 CA 41171-03
Maximum Entropy Densities

148. ROSENBERG, Lynn
Boston University Sch. Med.
5 R37 CA 45762-02
Case-Control Surveillance of Serious Illnesses & Drugs

149. ROSNER, Bernard A.
Brigham & Women's Hospital
1 R01 CA 50597-01
Measurement Errors in Cancer & Respiratory Epidemiology

150. ROSS, Ronald K.
University of Southern California
5 P01 CA 17054-14
USC Cancer Center Epidemiology & Biostatistics Unit: TAT

151. ROSS, Ronald K.
University of Southern California
5 R01 CA 36388-05
Case-Control Study of Multiple Myeloma

152. ROSS, Ronald K.
University of Southern California
5 R01 CA 43092-03
Dietary Factors in the Etiology of Cancer

153. ROTHMAN, Kenneth J.
University of Massachusetts Med. Sch.
2 R01 CA 38455-03
Case-Control Study of Laryngeal-Hypopharyngeal Cancer

154. ROTTER, Jerome I.
Cedars-Sinai Medical Center
5 R01 CA 44688-03
Inheritance & Markers of Colorectal Cancer & Polyps

155. ROUSH, George C.
Preventive Med. Inst.-Strang Clin.
1 R03 CA 50326-01
Enzymatic Measures of Oxidative Stress and Breast Cancer

156. RYAN, Louise
Dana-Farber Cancer Institute
5 R29 CA 48061-02
Biostatistical Topics in Carcinogenicity & Teratology

157. SADOWSKI, James A.
Tufts University
1 R03 CA 44551-01
Measurement of Dietary Sodium, Potassium, & Nitrate

158. SANDLER, Robert S.
University of North Carolina
5 R01 CA 44684-02
Risk Factors for Colon Adenomas

159. SAUNDERS, L. Duncan
California Public Health Fdn.
5 R01 CA 48288-02
AIDS & Cancer--New Insights Through Record Linkage

160. SAVITZ, David A.
Univ. of North Carolina, Chapel Hill
1 R03 CA 48908-01
Menstrual Cycle Patterns & Risk of Breast Cancer

161. SCHIMPA, Peter B.
I.S. Grupe, Inc.
1 R43 CA 50842-01
Epidemiology Information Resource on Optical Disk

162. SCHLESSELMAN, James J.
Henry M. Jackson Foundation
1 R01 CA 50193-01
Oral Contraceptives & Cancer

163. SHORE, Roy E.
New York University
5 R37 CA 43175-04
Follow-Up of Patients X-Irradiated for Scalp Ringworm

164. SHUKER, David E. G.
Int'l Agency Res. Cancer
5 U01 CA 48473-02
Excreted Alkyl Purines as Markers of In Vivo DNA Damage

165. SHY, Carl M.
University of North Carolina
1 R03 CA 47864-01
Micronuclei in Bronchial Cells of Uranium Miners

166. SKOLNICK, Mark H.
University of Utah
5 R01 CA 28854-08
Genetic Epidemiology of Cancer in Utah Genealogies

167. SLATTERY, Martha L.
University of Utah Med. Ctr.
5 R01 CA 40060-03
Passive Smoking as a Cervical Cancer Risk Factor

168. SPEIZER, Frank E.
Brigham & Women's Hospital
5 R37 CA 40356-05
Prospective Study of Diet & Cancer in Women

169. SPEIZER, Frank E.
Brigham & Women's Hospital
1 R01 CA 49449-01
Biochemical Markers in the Nurses' Health Study Cohort

170. SPITZ, Margaret R.
Univ. of Texas System Cancer Ctr.
1 R03 CA 50945-01
Environmental & Genetic Interactions in Risk of Aerodigestive Tract Cancer

171. STEBBINGS, James H.
University of Chicago
5 R01 CA 40071-02
Dose Interactions of Passive Smoking with Domestic Radon

172. STOCKWELL, Heather G.
University of South Florida
5 R29 CA 45513-03
Epidemiology of Lung Cancer in Non-Smoking Women

173. STORER, Barry E.
University of Wisconsin
5 R29 CA 45313-02
Biostatistical Methods for Cancer Research

174. STROM, Brian L.
University of Pennsylvania
3 R01 CA 35934-03S1
Biochemical Epidemiology of Biliary Tract Cancer

175. STRONG, Louise C.
University of Texas System Cancer Ctr.
5 P01 CA 34936-06
A Mutational Model for Childhood Cancer

176. STRONG, Louise C.
University of Texas System Cancer Ctr.
5 R01 CA 38929-05
Genetic Epidemiology of Childhood Sarcoma

177. STRONG, Louise C.
University of Texas System Cancer Ctr.
2 R03 CA 47648-02
Genetic Epidemiology of Childhood Brain Tumors

178. SWIFT, Michael R.
University of North Carolina
5 R01 CA 14235-16
Neoplasia-Predisposing Genes of Man

179. SYME, S. Leonard
University of California, Berkeley
1 R03 CA 44445-01
Race, Class, & Age-Specific Breast Cancer Incidence

180. TANNER, Martin A.
University of Wisconsin, Madison
2 R01 CA 35464-06
Nonparametric Analysis of Censored Data

181. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
2 R37 CA 41530-04
Trace Elements & Cancers of Larynx, Esophagus & Mouth

182. THOMAS, Duncan C.
University of Southern California
5 R01 CA 42949-03
Time Related Factors in Cancer Epidemiology

183. THOMSEN, Donald L.
Societal Inst. of the Math. Sci.
1 R13 CA 49640-01
SIMS Conference--Scientific Issues-Quantitative Cancer

184. TREVISAN, Maurizio
State Univ. of New York, Buffalo
1 R03 CA 49426-01
A Diet Instrument for a Population with Varied Intakes

185. TSIATIS, Anastasios A.
Dana-Farber Cancer Institute
5 R01 CA 36446-06
Early Stopping of Clinical Trials

186. VALANIS, Barbara G.
Kaiser Foundation Hospitals
5 R01 CA 47727-02
Health & Occupational Exposure to Anti-Cancer Drugs

187. VANDERLAAN, Martin
Laurence Livermore Nat'l. Lab.
5 U01 CA 48446-02
Biochemical Measures of Exposure to Dietary Carcinogens

188. VAUGHAN, Thomas L.
Fred Hutchinson Cancer Res. Ctr.
5 R29 CA 46552-02
An Epidemiological Study of Nasopharyngeal Cancer

189. WANG, Helen H.
Beth Israel Hospital
5 R03 CA 48744-02
Epidemiology of Lymphomatoid Papulosis

190. WEI, Lee-Jen
University of Michigan, Ann Arbor
5 R01 CA 45544-03
Nonparametric Statistical Methods in Cancer Research

191. WEISS, Noel S.
University of Washington
5 R35 CA 39779-05
Research in Cancer Epidemiology

192. WESTHOFF, Carolyn L.
Columbia University
1 R03 CA 47827-01
Ca-125 Levels in Blood of Normal Women

193. WHITE, Emily
Fred Hutchinson Cancer Res. Ctr.
5 R29 CA 44790-03
Epidemiology of Physical Activity & Colon Cancer

194. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 23214-11
Effects of Multiple Exposures: Quantitative Aspects

195. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 45247-02
Reproductive Factors, Body Size, & Breast Cancer Risk

196. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 47247-02
Combined Analysis of Ovarian Cancer Case-Control Data

197. WHITTEMORE, Alice S.
Stanford University
1 R35 CA 47448-01A1
Research in Cancer Epidemiology & Biostatistics

198. WHITTEMORE, Alice S.
Stanford University
1 R01 CA 49446-01
Prostate Cancer in High, Medium, and Low Risk Populations

199. WIENCKE, John K.
University of California
5 R01 CA 43764-03
Mutagen Sensitivity in High Breast Cancer Risk Patients

200. WILLETT, Walter L.
Harvard University
5 R01 CA 40429-04
Nutritional Determinants of Breast Cancer Risk

201. WILLETT, Walter L.
Brigham & Women's Hospital
5 R01 CA 42059-04
A Cohort Study of Trace Elements & Cancer in Women

202. WILLETT, Walter C.
Harvard University
5 R03 CA 47446-02
Validation of a Mexican Food Questionnaire

203. WILLETT, Walter C.
Harvard School of Public Health
1 R01 CA 50385-01
Risk Factors for Breast Cancer Among Young Nurses

204. WILLETT, Walter C.
Brigham & Women's Hospital
1 R03 CA 51185-01
A Prospective Study of Diet & Colorectal Ademomas

205. WOOLSON, Robert F.
University of Iowa
5 R01 CA 39065-05
Epidemiologic Methods for Case-Control/Ecologic Studies

206. WYNDER, Ernst L.
American Health Foundation
5 P01 CA 32617-08
Interdisciplinary Studies in Cancer Epidemiology

207.	YU, Mimi C. University of Southern California 2 R01 40468-04A1	Salted Fish & Nasopharyngeal Carcinoma
208.	ZELEN, Marvin Dana-Farber Cancer Institute 5 R01 CA 23415-12	Statistical Models of Biomedical Phenomena
209.	ZIMMERMAN, Stuart O. Univ. of Texas System Cancer Ctr. 5 R01 CA 11430-23	Biomathematics & Computing in a Cancer Institute

CONTRACTS ACTIVE DURING FY 89

	Investigator/Institution/Contract	Title
210.	BATTISTE, E. C. C. Abaci, Inc. N43 CP 95629	Scientific Distribution Function Software for Biostatistical Operation
211.	BECKER, David S. I.S. Grupe, Inc. N43 CP 95640	Develop a CD-ROM of Mortality Data
212.	BOSTROM, Alan Crunch Software Corp. N43 CP 95628	A Microcomputer Program for Calculation of Probabilities, Percentiles & Power Analysis for Selected Distributions
213.	BOWEN, Kenneth A. Applied Logic Systems N44 CP 61026	User-Friendly Software for the Personal Computer (Bibliographic)
214.	BUNOW, Barry J. Civilized Software, Inc. N43 CP 95635	Generation of Biostatistical Distributions
215.	CASE, George D. Resource Technologies Group, Inc. N43 CP 95641	Portable Biochemical Detector for Carcinogen Exposures
216.	DETELS, Roger University of California, Los Angeles N01 AI 32511	Natural History of AIDS in Homosexual Men
217.	GRAVELY, Ben T. Triangle Research & Devel. Corp. N43 CP 95630	A Rugged Bar Code Labeling System for Extreme Environments

218.	HARE, David L. AMGEN, Inc. N43 CP 95636	Expression of Synthetic DNA Sequences Encoding the HTLV-1 Envelope Protein in E. coli
219.	IYPE, P. Thomas Biological Res. Facul. & Facil., Inc. N44 CP 85648	Antibody-Mediated Detection Systems for Acrolein: DNA Adducts
220.	JOHNSON, Norman L. Takima International Corp. N43 CP 95639	A Southeast Regional Cancer Registry
221.	KOKIKO, Elaine M. Moshman Associates, Inc. N01 CP 71017	Development of a Pre-1979 National Death Index
222.	KRIOZERE, Richard Med/Graphics Div., Lord Label & Mfg. N43 CP 95637	Bar Coded Sample Tracking/Collection System
223.	LATER, Douglas W. Lee Scientific N44 CP 71086	Biochemical Monitoring of Pesticides & their Metabolites by Supercritical Fluid Chromatography
224.	MAULUCCI, Ruth A. MOCO, Inc. N43 CP 95632	Microcomputer Generated Statistical Tables
225.	MAURITSEN, Robert H. Statistics & Epidemiology Res. Corp. N44 CP 61035	User-Friendly Software for the Personal Computer (Statistical)
226.	MEHTA, Cyrus R. Cytel Software Corp. N43 CP 95627	Electronic Tables for Statisticians
227.	POLK, B. Frank Johns Hopkins University N01 AI 32520	Natural History of AIDS in Homosexual Men
228.	RINALDO, Charles R., Jr. University of Pittsburgh N01 AI 32513	Natural History of AIDS in Homosexual Men
229.	SAILER, Peter Internal Revenue Service Y01 CP 50500	Test of the Usefulness of IRS Occupation Codes in Determining Mortality Differentials through the CWHS

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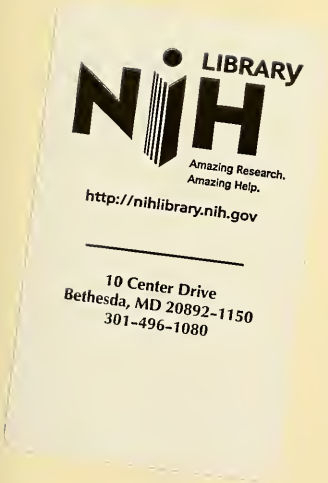

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