Division of

CANCER ETIOLOGY

1985 Annual Report Volume III
October 1, 1984-September 30, 1985

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

National
Institutes of
Health

National
Cancer
Institute

Bethesda,
Maryland 20892

National Cancer Institute

ANNUAL REPORT

DIVISION OF CANCER ETIOLOGY

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

TABLE OF CONTENTS

OFFICE OF THE DIRECTOR (VOLUME I)		Page No.
Director's Overview		
Administrative Highlights		1
Scientific Highlights		8
Activities in the Office of the Director		47
International Agreements and Information Exchange Activities		53
Project Reports:		
CP 03509	Carcinogenesis Chemotherapy and Biological Markers in Nonhuman Primates	60
CP 04548	Registry of Experimental Cancers/ WHO Collaborating Center for Tumours of Laboratory Animals	72
CP 06134	Role of Lymphatic System in the Absorption and Distribution of Antitumor Agents	76

Laboratory of Cellular and Molecular Biology

Summary Report 81
Contract Narratives 91

Project Reports:

CP 04930	Biology of Natural and Induced Neoplasia	92
CP 04940	Viruses and Transforming Genes in Experimental Oncogenesis and Human Cancer	97
CP 04941	Biochemical Characterization of Retroviruses and *onc* Genes	108
CP 04951	Molecular Characterization of Retroviruses	114
CP 04976	Carcinogenesis of Mammalian Cells in Culture	119
CP 04977	DNA Damage, Repair, and Neoplastic Conversion in Cultured Mouse and Human Cells	126
CP 05060	Studies of Oncogenic Expression in Animal and Human Cancers	131
CP 05062	Transforming Genes of Naturally Occurring and Chemically Induced Tumors	137
CP 05063	Studies on Epstein-Barr Virus and *Herpesvirus Saimiri*	142
CP 05164	Interaction of Hematopoietic Cells and Mammalian Retroviruses	148
CP 05167	Mechanisms of Transformation Induced by Retrovirus *onc* Genes	154
CP 05234	Molecular Cloning and Characterization of Transforming Genes	160
CP 05306	Properties of Human *ras* Oncogene-encoded Transforming Protein	163
CP 05307	Expression of Normal Human *sis*/PDGF-2 Coding Sequence Induces Transformation	166
CP 05308	Role of the *sis* Proto-oncogene in Human Malignancies	170

Page No.

CP 05362 Studies of Oncogene Expression During Cellular Growth and Differentiation 174

CP 05363 Analysis of Oncogenes Encoding a Growth Factor and Putative Receptor 178

CP 05365 Studies of Oncogenes in Human Urinary Tract Tumors 182

CP 05366 Studies on the Mechanisms of Oncogene Activation in Human Tumors 185

CP 05456 Tranformation Induced by Viral and Cellular fgr Oncogenes 189

CP 05457 Molecular Cloning of the Subunits of Platelet-Derived Growth Factor 192

CP 05458 Gene Organization of Human c-fgr and Its Related Sequences 196

CP 05459 Structural and Functional Characterization of ras p21 Proteins 199

CP 05460 Molecular Characterization of c-sis/PDGF-2 Locus 202

CP 05461 Regulation of c-sis Expression 205

CP 05462 Molecular Genetic Analysis of ras Genes 208

CP 05463 Cellular and Oncogene Products which Participate in Growth Regulation 211

CP 05464 Characterization and Subcloning of a New Human Oncogene 214

Laboratory of Molecular Oncology

Summary Report 217

Project Reports:

CP 04876 Oncogenic Virus Influence on the Biochemical Events of Host Cells 226

CP 04899 Transforming Genes of Avian RNA Tumor Viruses 229

CP 04963 Toward a Molecular Description of Malignant Transformation by p21 ras Oncogenes 242

		Page No.
CP 04970	Biochemistry of Cellular Transformation by Avian Tumor Viruses	249
CP 05120	Expression of Retroviral and Oncogene Proteins in Bacterial and Mammalian Vectors	254
CP 05186	Expression and Regulation of Viral and Cellular Oncogenes	262
CP 05238	The Transforming Genes of Acute Leukemia Viruses and Their Cellular Homologues	272
CP 05239	Structural Analysis of the Avian Carcinoma Virus MH2	277
CP 05286	Transforming Genes in Human Tumors and Chemically Transformed Human Cells	282
CP 05288	Control of Development Gene Expression - Chromatin Structure of Active Genes	287
CP 05294	Human Teratocarcinoma Cell Line, PA-1, as a Model System for Malignant Progression	294
CP 05295	Studies on the Activation of onc Genes in Viruses and Human Tumors	298
CP 05342	Expression of mos Gene at Elevated Levels	304
CP 05344	Studies of Cellular DNA Sequences Required to Transform Human Cells	307
CP 05359	Characterization of the p21 ras Oncogene Product	314
CP 05360	Studies on Retroviral and Cellular Oncogenes	318
CP 05361	Cell Interaction, cAMP and Control of Developmental Gene Expression	322
CP 05439	Protein Chemistry of p21 Biosynthesis and Processing	331
CP 05440	Site-Directed Mutagenesis of ras Oncogenes	334
CP 05441	Characterization of the Gene Product of the c-myc Locus	337
CP 05442	Involvement of c-ets in the Pathogenesis of Human Leukemias	341

Page No.

CP 05443 Oncogene Expression During Cell Differentiation and Development 344

CP 08718 Transcriptional and Post-transcriptional Control of the Lambda *Int* Gene Expression 349

Laboratory of Molecular Virology

Summary Report 353

Project Reports:

CP 05101 Studies on the Molecular Mechanisms for Malignant Transformation of Cells 355

CP 05214 Genetic Elements Regulating the Initiation of Transcription 358

CP 05216 *Ras* Oncogene Regulation in Yeast 361

CP 05217 Studies on the Regulation of SV40 Gene Expression 365

CP 05219 Construction of a Prokaryotic Vector for the Expression of Mammalian Proteins 368

CP 05220 Studies on the Structure and Function of Cell Surface Antigens 371

CP 05254 Regulation of Insulin Gene Expression 375

CP 05354 Studies on the Activated Form of the Human Proto-oncogene, c-Ha-*ras* 377

CP 05355 Regulation of Immune Surveillance Against Tumor Cells 380

CP 05390 How Do Tumor Cells Escape Immune Surveillance? 383

CP 05391 In Vitro Transcription Analysis of the SV40 Late Promoter 386

CP 05392 Transcriptional Rgulation of SV40 Late Transcription by Large T-Antigen 389

Page No.

CP 05393 Tissue-Soecific Activation of Gene Expression 392

CP 05394 Enhancer Elements in B-Lymphocytes and T-Lymphocytes 394

Laboratory of Tumor Virus Biology

Summary Report 397

Project Reports:

CP 00543 Characterization of the Papilloma-viruses 400

CP 00547 The Use of Papillomavirus DNAs as Eukary-otic Cloning Vectors 406

CP 00564 Early Events in Virus/Host Cell Interaction 410

CP 00565 Cell Immortalization and Transformation by Papovaviruses 413

CP 00898 Role of Human Papillomaviruses in Human Carcinogenesis 416

CP 05420 Transformation by Polyomaviruses 420

Laboratory of Viral Carcinogenesis

Summary Report 425

Project Reports:

CP 05150 Isolation of New Oncogenes 432

CP 05180 Evolution and Sequence Organization of Mammalian Retroviruses 436

CP 05330 Urinary Growth Factors in Human Neoplasia 440

CP 05333 Evolutionary Relationships of the Felidae: A Mitochondrial DNA Approach 445

CP 05358 The Role of Retroviruses in Simian AIDS and Retroperitoneal Fibromatosis 449

CP 05367 The Genetic Structure of Natural Popu-lations of Past and Present 453

Page No.

CP 05382 Genes Involved in Preneoplastic Progression 460

CP 05383 Membrane Signal Transduction in Tumor Promotion 467

CP 05384 Genetic Analysis of Human Cellular Genes in Neoplastic Transformation 472

CP 05385 Molecular Genetic Analysis of Feline Cellular Genes: A Comparative Approach 478

CP 05386 Basic Mechanisms in HTLV-Induced Leukemia and AIDS 484

CP 05387 Characterization of the raf Oncogene 489

CP 05388 Molecular Basis of Induction of Neoplasia by the Oncogene myc 492

CP 05389 Development of Reproductive Endocrine-Genetic Strategies in Animal Species 496

CP 05401 Molecular Basics of Retroviral Transcriptional Transactivation 504

CP 05404 Growth Modulation of raf Associated Tumors 508

CP 05414 Etiology and Prevention of Simian Acquired Immune Deficiency Syndrome (SAIDS) 511

CP 05417 Molecular and Functional Characterization of the raf Oncogene Group 518

CP 05418 Interaction between raf and myc Oncogenes in Transformation In Vitro and In Vivo 523

CP 05419 Expression of raf/myc Recombinant Viruses - Cooperative Oncogenes 528

Biological Carcinogenesis Branch

Summary Report 533
Grants Active During FY 85 548

DNA Virus Studies I

Summary Report 550
Grants Active During FY 85 557
Contracts Active During FY 85 564

Page No.

DNA Virus Studies II

Summary Report 565
Grants Active During FY 85 572

RNA Virus Studies I

Summary Report 579
Grants Active During FY 85 593

RNA Virus Studies II

Summary Report 602
Grants Active During FY 85 611

Research Resources

Summary Report 619
Contracts Active During FY 85 623

CHEMICAL AND PHYSICAL CARCINOGENESIS PROGRAM (CPCP) (VOLUME II)

Laboratory of Biology

Summary Report 625

Project Reports:

CP 04629 Regulation of Stages of Carcinogenesis Induced by Chemical or Physical Agents 630

CP 04673 The Immunobiology of Carcinogenesis 645

Laboratory of Cellular Carcinogenesis and Tumor Promotion

Summary Report 651

Project Reports:

CP 04504 Model Systems for the Study of Carcinogenesis at the Cellular Level 660

CP 04798 Metabolism and Mode of Action of Vitamin A 673

CP 05177 Use of Immunological Techniques to Study Interaction of Carcinogens with DNA 688

Page No.

CP 05178 Cellular and Tissue Determinants of Susceptibility to Chemical Carcinogenesis 695

CP 05270 Molecular Mechanism of Action of Phorbol Ester Tumor Promoters 701

CP 05445 Molecular Regulation of Epidermal Specific Differentiation Products 713

Laboratory of Chemoprevention

Summary Report 725

Project Reports:

CP 05051 Mechanism of Action of Type Beta Transforming Growth Factor 728

CP 05267 Identification and Action of Platelet-derived Transforming Growth Factor-beta 733

CP 05396 Development of Analogs for Study of Oncogenesis and Development of the Rat 736

CP 05397 Role of Ectopic Peptides in Phenotypic Transformation 739

CP 05398 Functional Characterization of Transforming Growth Factors and Their Receptors 744

Laboratory of Comparative Carcinogenesis

Summary Report 749

Project Reports:

CP 04542 Chemistry of N-Nitroso Compounds 759

CP 04580 The Role of Lipotropes in Carcinogenesis 772

CP 04582 Metal Interactions in Carcinogenesis 776

CP 04680 Application of In Vitro Systems to Study Perturbations of Methyl Metabolism 780

CP 04812 Cell Interactions During Transformation of Epithelial Cells 784

CP 05092 Transplacental Carcinogenesis and Tumor Promotion in Nonhuman Primates 789

CP 05093 In Vitro Studies on Organ Specificity in Transplacental Carcinogenesis 797

Page No.

CP 05299 Interspecies Differences in Transplacental Carcinogenesis and Tumor Promotion 803

CP 05301 Biology and Pathology of Natural and Experimentally Induced Tumors 808

CP 05303 Pathogenesis and Promotion of Natural and Induced Tumors 812

CP 05350 The Thymic Microenvironment During T-Cell Lymphoma Development 818

CP 05351 Ultrastructural Pathology: Morphological Analysis of Natural Killer Cell Activity 821

CP 05352 Metabolic and Pharmacological Determinants in Perinatal Carcinogenesis 824

CP 05353 Sensitivity Factors in Special Carcinogenesis Models 829

CP 05399 Oncogene Expression in Chemically Induced Tumors 834

CP 05465 The Regulatory Role of Retinoids on the Development of the Avian Embryo 838

Laboratory of Experimental Carcinogenesis

Summary Report 843

Project Reports:

CP 04986 Molecular Basis of Steroid Hormone Action 871

CP 05260 Regulation of Gene Expression and Differentiation in Neoplasia 875

CP 05261 Metabolism and Mutagenicity of Chemical Carcinogens 880

CP 05262 Cellular Evolution of Chemically Induced Murine Hepatomas 885

CP 05263 Computer Analysis of Carcinogenesis by Two-Dimensional Gel Electrophoresis 889

CP 05283 Transmission of Mammalian Genes with Expression-Regulated Retrovirus Vectors 895

CP 05313 Early Events in Chemically Induced Rat Hepatocarcinogenesis 898

		Page No.
CP 05315	Cell Surface Proteins and Cellular Adhesion in Hepatocarcinogenesis	904
CP 05370	Normal Stem Cell Biology and Hemopoietic Regulation	907
CP 05371	Analysis of Direct Actions of Transforming Proteins of Oncogenic Viruses	910
CP 05373	Purification of Rat Hepatic Proliferation Inhibitor (HPI)	913
CP 05374	Structural and Physicochemical Studies of Proteins Relevant to Tumorigenesis	917
CP 05375	Effect of Chemical Leukemogens on Hemopoietic Target Cells	922
CP 05378	Hormone-Dependent Transcriptional Regulatory Elements: Structure and Function	925
CP 05379	Analysis of Polypeptide Changes During Cellular Differentiation and Transformation	928
CP 05446	Initiation and Termination of Hepatocyte Proliferation by Serum Factors	933
CP 05447	Isolation and Characterization of Proteins from Two-Dimensional Polyacrylamide Gels	936
CP 05448	Guanosine Triphosphate Binding Site of Ras Protein by NMR and CD Spectroscopy	940
CP 05449	Conformational Studies on Epidermal Growth Factor and Transforming Growth Factor	943
CP 05450	Chromatin Structure and Steroid Hormone Action	946
CP 05451	Hepatocellular Carcinoma: Expression of Retroviral Associated Oncogenes	949
CP 05452	Gene Expression and Development in Transgenic Mice	954
CP 05453	Chemical Carcinogenesis; Transformation with Viral Oncogenes; Tumor Progression	957
CP 05454	Chemical Transformation of Human Lymphoblastoid Cell Lines	960

Page No.

CP 05455 Molecular Cloning of Genes Associated with Chemical Hepatocarcinogenesis 964

Laboratory of Experimental Pathology

Summary Report 969

Project Reports:

CP 04491 Quantitative Studies on Concurrent Factors in Neoplastic Transformation 985

CP 04493 Bioenergetic Pathways in Chemically-Transformed Epithelial Cells 989

CP 05265 Effects of Chemical Carcinogens on Transforming DNA Sequences and Expression 994

CP 05273 Molecular Mechanisms in Multistage Carcinogenesis 1000

CP 05274 Respiratory Carcinogenesis by Chemical and Physical Factors 1005

CP 05276 Growth Control in Epithelial Cells and Its Alteration in Carcinogenesis 1015

CP 05381 Cellular/Molecular Stages of Carcinogenesis in Respiratory Epithelia 1026

Laboratory of Human Carcinogenesis

Summary Report 1031
Contract Narratives 1052

Project Reports:

CP 04513 Metabolism of Chemical Carcinogens by Cultured Human Tissues and Cells 1065

CP 05192 Repair of Carcinogen-Induced Damage in Human Cells 1071

CP 05193 Growth and Differentiation of Normal Human Epithelial Cells and Carcinoma Cells 1076

CP 05291 DNA Adducts in People Exposed to Polycyclic Aromatic Hydrocarbons 1086

		Page No.
CP 05293	Oncogene Transfection of Human Cells	1090
CP 05324	Human Lung Carcinoma/Bronchial Epithelial Cell Hybrid Genetics	1094
CP 05325	DNA Cytosine Methylation and Cellular Physiology	1097
CP 05326	HLA Antigens: Structure, Function and Disease Association	1101
CP 05327	Development and Use of Antibodies to Detect Carcinogen-DNA Adducts	1106
CP 05328	Immunologic Studies of Human T-Cell Lymphoma Virus	1110
CP 05341	Cytopathology of Asbestos and Other Fibers on Human Lung Cells in Culture	1115
CP 05403	Molecular Analysis of Gene Regulation and Proliferative Control in Human Cells	1120
CP 05408	Drug Metabolism Phenotyping of Nonhuman Primates	1123
CP 05409	Control of Growth and Differentiation of Human Bronchial Epithelial Cells	1127
CP 05410	Hepatitus B Virus Carcinogenesis	1132
CP 05413	Enzyme Immunoassay for Endogenous N-Nitrosation Products	1136
CP 05421	Genetic Transfection of Human Cells	1139
CP 05422	Compounds Modifying Growth and Differentiation of Human Esophageal Cells	1144
CP 05423	Specific Binding of [3H] Phorbol 12,13-Dibutyrate to Human Esophageal Cells	1147
CP 05424	The Role of Respiratory Viruses in Lung Carcinogenesis	1150
CP 05425	Asbestos Carcinogenesis/Chromosomal Changes in Human Cells	1153
CP 05426	Characterization, Mode of Action, and Evolution of the Oncogene Raf	1156
CP 05427	Human Chorionic Gonadotropin as a Marker and Growth Factor in Human Lung Tumors	1163

		Page No.
CP 05428	Genomic Libraries from A1146, Human Bronchial Epithelial Cells and Fibroblasts	1167
CP 05429	Use of Retroviral Shuttle Vector for Infection of Oncogenes into Human Cells	1170
CP 05430	Substracted cDNA Cloning and Substracted cDNA Probes	1173
CP 05431	Transfection of Oncogenes into Human Bronchial Epithelial Cells (NHBE)	1175
CP 05432	The Biological Activity of Fecapentaene-12 in human Tissue Cells	1178
CP 05433	Synchronous Fluorescence Scanning Detection of Aflatoxin Adducts	1181
CP 05434	The Immunobiology of AIDS and AIDS-Related Diseases	1185
CP 05435	Analysis of Hydrocarbon-DNA Adducts in Humans and Relation to Cancer Risk	1190

Laboratory of Molecular Carcinogenesis

Summary		1195
Project Reports:		
CP 04496	Chromosomal Proteins and Chromatin Function	1202
CP 04516	Cellular and Molecular Effects of Psoralen Plus Ultraviolet Light	1207
CP 04517	DNA Repair in Human Cancer-Prone Genetic Diseases	1210
CP 04525	Studies on Electrophoretic Techniques for Protein, RNA, and DNA	1215
CP 04578	Structure and Expression of Human Actin Genes	1218
CP 04785	DNA Repair Studies on Human and Mouse Normal, Tumor and Transformed Cells	1221
CP 05086	Monoclonal Antibodies to Cytochrome P-450 from Human Tissue	1226

Page No.

CP 05109 Chromatin Structure and Carcinogenesis 1230

CP 05125 Preparation of Monoclonal Antibodies to Cytochromes P-450 1234

CP 05196 Cloning and Characterization of Human Cytochrome P-450 1238

CP 05204 Carcinogen-induced Mutagenesis of a Shuttle Vector Plasmid in Human Cells 1241

CP 05205 Naturally Occurring Inhibitors of Different Forms of Cytochrome P-450 1244

CP 05208 Phenotyping of Cytochrome P-450 in Human Tissues Using Monoclonal Antibodies 1247

CP 05317 Opal Suppressor tRNA Genes in Human, Chicken, Rabbit and Xenopus Genomes 1250

CP 05318 Immunopurification and Characterization of Cytochrome P-450 1254

CP 05339 Radioimmunoassay of Cytochromes P-450 Using Monoclonal Antibodies 1258

CP 05436 The Role of Mouse Cytochrome P1-450 and P3-450 in Carcinogenesis 1261

CP 05437 Transcription Regulatory Elements in the Mouse Cytochrome P-450 Gene 1264

CP 05438 Experimental Model Systems for Human Colon Cancer 1267

Chemical and Physical Carcinogenesis Branch

Summary Report 1271

Biological and Chemical Prevention

Summary Report 1281
Grants Active During FY 85 1287
Contracts Active During FY 85 1292

Carcinogenesis Mechanisms

Summary Report 1293
Grants Active During FY 85 1302

Page No.

Diet and Nutrition

Summary Report 1310
Grants Active During FY 85 1314

Molecular Carcinogenesis

Summary Report 1317
Grants Active During FY 85 1346

Smoking and Health

Summary Report 1364
Grants Active During FY 85 1369
Contracts Active During FY 85 1370

Chemical Research Resources

Summary Report 1371
Contracts Active During FY 85 1375

Low Level Radiation Effects Branch

Summary Report 1377
Grants Active During FY 85 1385
Contracts Active During FY 85 1390

EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM (VOLUME III)

Report of Associate Director 1393

Biostatistics Branch

Summary Report 1405
Summary Report of Progress on Research Contracts 1414
Research Contracts Active During FY 85 1415

Project Reports:

CP 04265 Consulting in Statistics and Applied Mathematics 1416

CP 04267 Research in Mathematical Statistics and Applied Mathematics 1422

CP 04269 Biomedical Computing - Consultation, Research and Development, Service 1426

CP 04475 Skin Cancer and Solar Radiation Program 1432

Page No.

CP 04500 Methodologic Studies of Epidemiology 1437

CP 04779 Field Studies in High Risk Areas 1443

Clinical Epidemiology Branch

Summary Report 1453

Project Reports:

CP 04377 Familial, Congenital and Genetic Factors in Malignancy 1467

CP 04400 Clinical Epidemiology of Cancer 1484

CP 05139 NIH Interinstitute Medical Genetics Program: The Genetics Clinic 1489

CP 05146 Morbidity in Childhood Cancer Survivors and Their Offspring 1493

CP 05194 National Cancer Mortality Studies by Computer 1497

CP 05279 Development of Epidemiologic Data Resources 1501

CP 05280 Carcinogenic Effects of Ionizing Radiation 1505

CP 05319 Epidemiologic Studies on Viruses and Genetics in the Etiology of Cancer 1508

CP 05329 Hepatitis B Virus and Liver Cancer in Army Veterans of WWII 1514

Environmental Epidemiology Branch

Summary Report 1517

Summary Reports of Progress on Research Contracts:

Environmental Studies Section 1533
Contracts Active During FY 85 1538

Population Studies Section 1539
Contracts Active During FY 85 1542

Project Reports:

CP 04378 U.S. Cancer Mortality Survey 1543

CP 04410 Studies of Persons at High Risk of Cancer 1547

Page No.

CP 04411 Cancer and Related Conditions in Domestic Animals: Epidemiologic Comparison 1561

CP 04412 Carcinogenic Effects of Therapeutic Drugs 1564

CP 04480 Studies of Occupational Cancer 1572

CP 04501 Case-Control Studies of Selected Cancer Sites 1582

CP 05128 Diet and Nutrition in Cancer Etiology 1595

CP 05400 Epidemiology of Human T-Cell Lymphotrophic Viruses: ATL, AIDS and Cancer 1608

Radiation Epidemiology Branch

Summary Report 1637

Summary Report of Progress on Research Contracts 1648
Contracts Active During FY 85 1654

Project Reports:

CP 04481 Studies of Radiation-Induced Cancer 1656

CP 05368 Studies of Drug-Induced Cancer and Multiple Primary Cancers 1688

Extramural Programs Branch

Summary Report 1699

Biometry Program

Summary Report 1705

Epidemiology Program

Summary Report 1707

Grants Active During FY 85 1721
Contracts Active During FY 85 1732

ANNUAL REPORT OF

THE EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

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

Dr. Joseph F. Fraumeni, Jr. continued to direct the Program as the Associate Director for Epidemiology and Biostatistics. Dr. William J. Blot was appointed this year as Chief of the Biostatistics Branch, which now includes the Analytical Studies Section (Chief, Dr. Blot) which was transferred from the Environmental Epidemiology Branch. In addition, an Epidemiologic Methods Section (Chief, Dr. Mitchell Gail) was created in the Biostatistics Branch along with an Information Resource Management Section (Chief, Mr. Michael Stump). The other components of the Program are the Environmental Epidemiology Branch (Chief, Dr. Robert N. Hoover), the Clinical Epidemiology Branch (Dr. Robert W. Miller), the Radiation Epidemiology Branch (Dr. John D. Boice, Jr.) and the Extramural Programs Branch (Chief, Dr. John A. Cooper). Thus, as a result of reorganization over the past two years, there are now four intramural branches and one extramural branch in the E&B Program. The Branch Chiefs have summarized in their annual reports the research activities taking place this year. In this report, the general orientation, summary highlights, and future direction of the E&B Program are briefly described.

Intramural Research

Continued emphasis was given this year to case-control and cohort studies aimed at evaluating key hypotheses in cancer etiology. Case-control studies of selected cancers have been undertaken when high-risk communities are identified on the cancer maps or when major testable hypotheses and special resources become available. Whenever possible, laboratory procedures are incorporated in the epidemiologic studies to better clarify exposures, preclinical responses, and mechanisms of carcinogenesis.

Tobacco: Cigarette smoking is known to account for a substantial proportion of human cancer, and its effects on lung cancer were evaluated by a large-scale case-control study in several European cities. The size of this study made it possible to clarify the modification of risk due to changing smoking habits. It was found that cessation of smoking lowers lung cancer risk, but the reduction was proportionally greater for short-term vs. long-term smokers. Little excess risk was seen among the group of persons who smoked for less

than 20 years and then quit for 10 or more years. Hence, the effect of smoking on lung cancer risk appears largely reversible if the habit is stopped soon enough. In addition, the risk for lifelong filter smokers was about one-half that seen for lifelong non-filter smokers. However, the risk for those who quit smoking for 10 or more years was much lower, being 20 to 30 percent of the risk seen among those who continued smoking. Although the dangers of filter cigarettes are less than non-filters, there was a substantial increase in the risk of lung cancer proportional to the duration of smoking filters. The European study was of sufficient size to dismiss the claims of some investigators that smoking affects only squamous and small-cell lung cancers. Among 938 patients with lung adenocarcinoma, risk increased in proportion to the duration and amount of smoking. Excess risks of lung cancer were also associated with cigar and pipe smoking, with dose-response relationships independent of cigarette smoking.

Tobacco habits and lung cancer risks vary geographically in the United States. A case-control study of lung cancer in a high-risk area of southern Louisiana implicated the heavy use by Cajuns of local brands and hand-rolled cigarettes containing high-tar levels. Because of an earlier study linking smokeless tobacco to high rates of oral cancer in the southern United States, the Program has become involved in additional projects to clarify the cancer risks associated with snuff dipping and chewing tobacco.

Several studies are evaluating the possible association of lung cancer with passive smoking. Preliminary data from a case-control study of lung cancer among non-smoking women suggest an increased risk, in proportion to the number of cigarettes their husbands smoked, and indicate the importance of further studies with more quantitative exposure data on various sources of environmental tobacco smoke. Finally, the impact of tobacco on cancer incidence appears to be increasing with newer understanding about the causes of particular tumors. Recently completed case-control studies of renal cell cancer, renal pelvis cancer, nasal cancer, and cervical cancer indicate etiologic relationships to cigarette smoking, so that the list of cancers associated with tobacco products continues to grow and the need for preventive action is more urgent than ever.

Occupation: As a time-tested means of identifying physical and chemical carcinogens, occupational studies were pursued to assess hazards suspected on the basis of experimental, clinical, and field observations. During the past year a case-control study of bladder cancer in New England uncovered an elevated risk among truck drivers that rose to nearly 2.5-fold among those employed for five or more years. The risk was greatest among men who began driving in the 1930s and 1940s and remained unchanged after controlling for smoking and coffee drinking. The high rate of bladder cancer in both sexes in this area was found to be related, in part, to exposures in the leather and textile industries. A survey of professional artists revealed excess mortality from leukemia and cancers of the bladder and kidney among painters, and cancer of the prostate among sculptors. The excess of bladder cancer among painters was confirmed in a reanalysis of data from the National Bladder Cancer Survey. This Survey also revealed excess risks among truck drivers (especially those using diesel engines), railroad workers, metal machinists, metal workers, construction workers, lumbermen and woodworkers, hair dressers, drycleaners and cutting operators.

A screening program for colorectal cancer and polyps by flexible sigmoidoscopy among pattern makers uncovered a 2.6-fold excess of colon cancer, but the excess could not be linked to any specific characteristic of pattern making. Compared to asymptomatic populations, the proportion of pattern makers with polyps did not appear excessive. A systematic survey of the mortality experience of 293,958 U.S. veterans by occupation/industry and smoking habits provided new clues regarding work-related factors that require further evaluation. Elevated risks for stomach cancer among carpenters, machinists, and steelworkers may reflect exposure to dusts and abrasives. Surveys of anatomists and morticians uncovered consistently elevated mortality from leukemia and brain cancer, and further projects to clarify the possible influence of formaldehyde in these and other formaldehyde-exposed groups are underway.

A case-control study of leukemia using death certificates uncovered associations between leukemias and farming-related activities. Case-control interview studies of leukemia, lymphoma, and soft-tissue sarcomas are underway to evaluate the role of herbicides, insecticides, and other agricultural factors in the origin of these tumors. A case-control study of nasal cancer in Virginia and North Carolina implicated occupational exposure to wood dust and textiles; the latter association may explain the high rates of nasal cancer among women in this area. A case-control study of renal pelvis cancer suggested the influence of occupational exposure to aromatic amines, which resembles the associations reported for bladder cancer.

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

A new survey of breast cancer among atomic bomb survivors revealed, for the first time, a dose-related excess risk among women exposed under age 10, indicating that the immature breast is susceptible to the carcinogenic effects of radiation. A study of childhood cancer in twins indicated a 2-fold excess risk associated with prenatal x-ray, suggesting that the association is due to radiation rather than the indications for pelvimetry. A case-control interview study found that 9% of all thyroid cancers could be attributed to prior childhood head and neck irradiation, and that pregnancy subsequent to radiation exposure appeared to enhance risk. A further follow-up of children irradiated for ringworm of the scalp in Israel revealed an excess of thyroid cancer and nodules following doses on the order of 9 rads, as well as elevated risks of brain tumor and leukemia.

In an international survey of cervical cancer, radiotherapy was found to be associated with a small, but significant, increased risk of leukemia. This may be related to the low doses of radiation absorbed by bone marrow outside the pelvis, since pelvic marrow was probably destroyed or rendered inactive by the large therapeutic exposures. Ovarian damage by radiation may have contributed to a low breast cancer risk, which was evident even among post-menopausal women. The expression period for radiation-induced solid tumors

appeared to continue to the end of life. Chromosome aberrations following partial-body irradiation were found to persist in circulating lymphocytes for over 30 years.

In an international study of over 9000 children treated for cancer, the risk of second cancers of the bone was strongly associated with high-dose radiation therapy. Radiotherapy was not associated with increased rates of second leukemias, which could be attributed almost entirely to alkylating agent treatment. A joint monograph on multiple primary cancers, focusing on long-term survivors, was prepared in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. Cancer patients in Connecticut were found to have a 31% increased risk of developing a second primary cancer, which rose to 49% among those surviving more than 30 years. Some constellations of cancers appeared to be due to smoking and alcohol (e.g., lung, larynx, esophagus, buccal cavity, and pharynx), whereas others seemed to be related to hormonal or dietary factors (e.g., colon, uterine corpus, breast, and ovary). In some instances, second cancers appeared to be caused by radiotherapy (e.g., rectal cancer following cancers of the female genital tract, and leukemia following uterine corpus cancer) or by chemotherapy (e.g., acute non-lymphocytic leukemia following multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary). The non-neoplastic effects of radiotherapy was examined in a registry of long-term survivors of childhood cancer at the Dana-Farber Cancer Center. Among Wilms' tumor survivors, an excess of low-birth weight was found among the offspring of females, but not males, suggesting a consequence of radiogenic fibrosis of the developing uterus.

Medications: Studies were continued to evaluate the carcinogenic effects of cytotoxic drugs, hormones, and other compounds. A survey of patients given methyl-CCNU, a nitrosourea used in cancer chemotherapy, provided the first quantitative evidence that the risk of developing a leukemic disorder was directly related to the total dose per surface area administered. Alkylating agents to treat childhood cancer were associated with an increased risk of leukemia and bone cancer--the latter provides evidence that solid tumors may result from chemotherapy. An analysis of cancer registry data suggested that women with breast cancer who received chemotherapy are prone to leukemia. In addition, women with breast cancer who received estrogen therapy were at an increased risk of endometrial cancer. Recent concerns about the possible tumor-promoting effects of thyroid supplements on breast cancer risk were not substantiated. Data from the Breast Cancer Detection Demonstration Project revealed an association between use of menopausal estrogens and the risk of benign breast disease of all histological types, with an increased risk associated with duration of use. Case-control studies revealed an increased risk of in situ and invasive cervical cancer associated with oral contraceptives, particularly with long-term use. This risk persisted after adjusting for sexual activity and smoking, which were independent risk factors. The use of phenacetin-containing analgesics was implicated in a case-control study of renal pelvis cancer, which also suggested the possible influence of acetoaminophen; this association deserves further study because of the increasing use of this drug.

Nutrition: Studies were further intensified this year as evidence accumulates to suggest that dietary factors contribute to a large though uncertain

fraction of human cancer. Several studies have utilized geographic areas in the United States (e.g., north/south differentials for large bowel cancer) and migrant groups (e.g., Japanese- and Norwegian-Americans) whose cancer risks may be altered by changing dietary habits. The role of dietary fat in colon cancer has been suggested, and a case-control study was begun to clarify the role of dietary patterns, in conjunction with laboratory measurements of blood and feces for lipids, fiber, micronutrients and mutagenicity in several bacterial systems. Dietary fat may also alter the risk of breast cancer, perhaps by increasing estrogen production. A case-control study of young Asian-American women with breast cancer has been started to clarify the role of nutritional and hormonal factors and their interactions. Fat intake and hormonal levels may contribute also to renal cell cancers, since a case-control study in Minnesota revealed that obesity was a risk factor in females, but not males. Women whose body mass index was in the highest 5% percent had a risk of 6-fold compared to those in the lowest 25%.

Evidence is mounting that a low intake of certain food groups may contribute to certain cancers. A case-control study of esophageal cancer in black males implicated a broad nutritional deficiency in addition to alcohol intake. A case-control study of oral cancer in southern women pointed to deficiencies in fruits and vegetables, resulting in low intake of micronutrients such as vitamin C and carotene. In a case-control interview study of lung cancer in New Jersey, males in the lowest quartile of carotenoid intake had increased risk compared to those in the highest quartile after adjusting for smoking. No reduction in lung cancer risk was associated with retinol or total vitamin A consumption. Vegetables afforded even more protection than the carotenoid index, particularly the consumption of dark yellow-orange vegetables, which have a high content of alpha- and beta-carotene relative to other carotenoids. The effect of vegetable intake was greatest for squamous-cell carcinomas, with the smoking and education-adjusted risk among low-consumers reaching 1.6 compared to high-consumers. This effect was limited to smokers of long duration and current smokers, suggesting action on a late stage or promotional event. Opportunities to study nutritional hypotheses are also being pursued in other countries, particularly China, where several collaborative case-control and intervention studies are underway. In addition, E&B investigators have continued to develop and utilize national resources, including HANES I, the first Health and Nutrition Examination Study of the United States, in efforts to relate dietary habits with the subsequent risk of cancer.

Genetic susceptibility: Enhanced by collaborative ties with laboratory investigators, epidemiologic and clinical observations have resulted in the delineation of familial cancer syndromes and several leads to mechanisms of host susceptibility. The discovery of the dysplastic nevus syndrome has provided a marker of susceptibility to melanoma, enabling early detection and treatment of this potentially lethal cancer. In fourteen families studied intensively over a seven year period, 42 new primary melanomas have been detected in 22 patients, and all but one was surgically curable. An analysis of the segregation of melanoma and dysplastic nevi in high-risk families indicate an autosomal dominant pattern of inheritance. The linkage observed between the melanoma phenotype and the Rh blood group, a genetically determinant polymorphic marker, provides additional evidence for dominant inheritance. It is noteworthy that the Rh gene is located on the short arm of

chromosome 1, which is the most frequently abnormal genomic segment in human melanoma tumor cells. Non-tumor fibroblast lines from patients with melanoma and dysplastic nevi have shown increased cell killing after exposure to ultraviolet light and to a UV-mimetic chemical.

Studies of a familial syndrome featuring soft-tissue sarcomas, breast cancer, and other neoplasms have led to the discovery of in vitro cellular radioresistance in this disorder. Preliminary cytogenetic studies of sarcomas indicate deletions or rearrangements in the region of 3p21, near the suspected gene locus for small-cell carcinoma of the lung. Study of a family with 10 cases of renal cell carcinoma has revealed a 3:8 translocation in the normal cells of all family members with renal carcinoma. The breakpoints seen on chromosomes 3 and 8 have prompted experimental studies into the role of chromosomal rearrangements and oncogenes. Preliminary findings suggest that the c-myc oncogene has been translocated without duplication in this family, and that sporadic renal cell cancers have non-random rearrangements in the short arm of chromosome 3. The repository of cancer-prone families in the Program has become of increasing interest to experimentalists involved in the identification of human oncogenes, and tissue specimens are made available upon request to the extramural community. The NIH Inter-Institute Medical Genetics Clinic, directed by two staff members, provides a multidisciplinary setting for studying families and individuals prone to cancer.

Environmental pollution: Epidemiologic studies have utilized relevant environmental measurements to evaluate the effects of pollutants in the general environment. To test the hypothesis that arsenical air pollution is related to lung cancer, a case-control interview study was carried out in the vicinity of a large zinc smelter in Pennsylvania. An elevated risk was found among people living near the smelter and in areas with high soil levels of arsenic, even after controlling for the effects of smoking and occupational exposure (excess risks were seen among long-term workers in the smelter and steel plant). The risk of indoor air pollution is being investigated through case-control studies of lung cancer in New Jersey and Sweden, where radon daughter products will be measured, and in China, where coal-burning stoves generate high levels of polycyclic hydrocarbons.

The risk of water pollution from halogenated hydrocarbons was evaluated by using the national case-control study of bladder cancer. Despite previous findings of an association based on geographic correlation studies, no overall relationship was found between drinking water quality and the risk of bladder cancer after making appropriate adjustments. However, in certain western areas (Iowa, New Mexico, and Utah), a positive association was detected between bladder cancer risk and duration of exposure to surface (chlorinated) water, suggesting the possible role of agricultural chemicals. Further case-control studies are planned to clarify the effect of water pollutants on the risk of bladder, colon, and other cancers, with particular attention to agricultural areas.

Infectious agents: Increasing attention was devoted to investigating the role of a type C retrovirus associated with a specific type of aggressive leukemia/lymphoma of T-cell origin. In collaboration with the NCI Laboratory of Tumor Cell Biology, a series of studies have clarified the relation of human T-cell lymphotropic virus type I (HTLV-I) to the T-cell malignancy. The

T-cell leukemias were found to occur primarily in areas where HTLV-I infection is endemic in the general population, such as southern Japan, the Caribbean basin, northern parts of South America, Central America, and certain parts of Africa and the Middle East. In the United States the cases have developed mainly in the black population of the southeastern United States, and in migrant groups from high-risk areas. In these widely separated parts of the world, a high percent of cases with T-cell leukemia have shown antibodies against HTLV-I. Within these endemic areas there appears to be marked variation in antibody prevalence, and the relatives of infected individuals have a much higher prevalence of antibodies than the surrounding population. Current emphasis is on the epidemiologic pattern of infection with this virus, including the identification of reservoirs, modes of transmission, and susceptibility states.

The Program has been heavily committed to investigating epidemic outbreaks of the acquired immunodeficiency syndrome (AIDS), which predisposes to Kaposi's sarcoma and opportunistic infections. Since HTLV-III is now implicated as a likely cause of AIDS, assays for this virus and T-cell subsets have been used in a series of epidemiologic studies of AIDS in the United States, Haiti, Denmark and Africa. Among male homosexuals and patients with hemophilia, the high risk of AIDS and AIDS-related complex has occurred almost exclusively among persons with this virus or its antibody. The finding of HTLV-III also clarified the previous known risk factors among male homosexuals; that is, multiple sexual partners, frequent anal receptive intercourse, and contact with individuals from high-risk areas. In the longitudinal study of hemophilia patients, the development of seropositivity with HTLV-III was primarily among patients given factor VIII concentrate, which is derived from a large number of blood donors. No evidence was found that HTLV-III was directly involved in the tumors associated with AIDS, notably Kaposi's sarcoma and lymphoma, but its immunosuppressive effect may trigger other mechanisms. Although the frequency of AIDS and HTLV-III infection is high in certain parts of Central Africa, no relation was found between the virus and the classical form of Kaposi's sarcoma, which is also endemic in this region. Also continued this year were studies to clarify the role of the Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal cancer, human papillomaviruses and herpes virus type II in cervical cancer, and hepatitis-B infection in primary liver cancer.

Biochemical epidemiology: Multidisciplinary projects combining epidemiologic and experimental approaches have been emphasized whenever possible to evaluate the influence not only of oncogenic viruses, but also of dietary and metabolic factors, host susceptibility, air and water pollutants, and a wide variety of other risk factors that are likely to escape detection unless laboratory probes are integrated with epidemiologic investigations. This approach, sometimes called biochemical or molecular epidemiology, has only recently been developed in cancer epidemiology. The laboratory parameters allow investigations to define past exposures and subclinical or preclinical response to initiators, promoters, and inhibitors of carcinogenesis, and to evaluate host-environmental interactions. The Program is seeking ways to utilize effectively this approach to clarify carcinogenic risks associated with nutritional influences or specific environmental agents that can be detected in tissues or body fluids. Opportunities are also being sought to assess specific host factors that influence susceptibility to cancer, including

endocrine function, immunocompetence, and genetic markers including oncogenes. Of special interest are techniques to detect and quantify exposure to particular carcinogens or their metabolites in vivo through chemical analyses, mutagenesis assays, or immunologic detection techniques. It is now possible to measure the interaction of certain agents with cellular target molecules, for example, through adduct formation with proteins and nucleic acids, excretion levels of excised adducts, and markers of altered gene expression. Collaborative studies with the NCI Laboratory of Human Carcinogenesis are being developed to investigate these mechanisms in lung cancer, and studies with the NCI Laboratory of Experimental Carcinogenesis and the Division of Cancer Treatment are underway to clarify the role of fecal mutagens in the development of colorectal cancer. Collaborations with other intramural laboratories are ongoing in viral carcinogenesis, especially to evaluate the role of retroviruses and papillomaviruses in human cancer.

Biostatistics: The Program continued to emphasize the development of basic and applied statistical methodology with applications to several areas, notably epidemiology and carcinogenesis research. Special attention was given to the development of multi-cause and multi-stage models of carcinogenesis, and to the clarification of issues involved in extrapolating results from experimental testing to the human experience. The Program co-sponsored a conference on the issue of time-related aspects of human carcinogenesis. Two staff members contributed extensively to the development of congressionally mandated "radioepidemiology tables," to be used as a guide for the probability of radiation being responsible for cancers among persons exposed to radioactive fallout. The Program continued to be responsible for statistical support and consultation to intramural scientists throughout the Institute, ranging from basic laboratory research to community activities in cancer control. With the expansion of applied prevention programs in the Division of Cancer Prevention and Control (DCPC), efforts were made to share epidemiologic resources and conduct collaborative projects, particularly in the area of diet and nutrition, and in the utilization of the Surveillance, Epidemiology, and End Results (SEER) Program for a wide variety of descriptive and analytical studies of cancer etiology and prevention.

Collaborative Activities

Interagency programs: Collaborative studies with other Federal agencies continued to receive high priority to: (1) evaluate urgent issues including those of immediate regulatory or public policy concern, and (2) stimulate the epidemiologic application of technical and data resources that are used by the Government mainly for other purposes. Although many research and regulatory agencies are concerned with environmental causes of cancer, few have epidemiologic programs and require assistance and support on many issues. Particularly at this time of fiscal constraint, it is important to increase initiatives to develop and coordinate national data resources that, with appropriate safeguards, may be tapped by qualified investigators throughout the country. During the year, staff members were active in the further development and adaptation of the National Death Index (NDI), located at the National Center for Health Statistics (NCHS). Efforts are being made to retroactively extend coverage of mortality before 1979 when the NDI began. Record-linkage studies have been planned in efforts to modify and utilize data on occupational exposure and cancer mortality from several agencies, including

the Social Security Administration (SSA), Internal Revenue Service (IRS), Bureau of the Census, and NCHS. Staff members also provided advice on modifying the internal revenue code to increase opportunities for epidemiologic studies of occupational groups, and on finding ways for agencies to exchange data and ease limitations on the appropriate research uses of individually identifiable records. Progress was made in obtaining from the SSA essential information for follow-up studies, and efforts are continuing to permit redisclosure of SSA information to the IRS for research purposes. Research using Veterans Administration hospital indices is underway along with record-linkage systems utilizing population-based cancer incidence registries.

International projects: Binational programs offer major epidemiologic opportunities for international study, and this year continued emphasis was given to joint studies and exchange programs with Chinese scientists to pursue clues drawn from the county-based maps in China. After completion of pilot investigations, case-control studies of cancers of the esophagus, lung, and stomach, and trophoblastic neoplasia are now underway in high-risk areas of China. In collaboration with DCPC, an intervention study is being conducted to evaluate the effect of micronutrients on the exceptionally high rate of esophageal cancer in Linxian. In Italy, a collaborative case-control study of stomach cancer is being planned to identify reasons for the very high rates in certain northern and central parts of that country. Staff members were also active in the U.S.-Japan program, coordinating workshops on the epidemiologic and etiologic aspects of cancers according to histologic type and adult-type cancers occurring under age 30. From many countries, guest investigators visited the Program for short but intense periods of collaborative research.

Other activities: Within the Program, further steps were taken to improve the coordination of epidemiology and biostatistics components, and to stimulate multidisciplinary activities linking epidemiologists with experimentalists. Through the mechanisms of the SEER program, cancer centers, prepaid health plans, and other resources, E&B staff became further involved in coordinating case-control and other analytical studies that involve collective approaches with pooling and sharing of data with outside investigators. In addition, several staff were involved this year with the preparation of several comprehensive and critical reviews, including the editing of volumes on radiation carcinogenesis, on multiple primary cancers, and on statistical methods in epidemiology. Service on interagency and other committees dealing with urgent public health and public policy issues was commonplace. For example, staff members contributed a chapter on epidemiology to a report of the Office of Science Technology and Policy (OSTP) dealing with principles of chemical carcinogenesis, served on an OSTP committee concerned with radiation research and policy coordination, chaired an interagency committee that oversees studies of the health effects of Agent Orange, served on committees of the National Council on Radiation Protection and Measurements dealing with prenatal effects of ionizing radiation and with the comparative carcinogenicity of radiation and chemicals, and contributed to several interagency committees concerned with particular chemical and physical hazards (e.g., asbestos, formaldehyde).

Although each group in the Program has its own specific mission and objectives, there is a great amount of interaction between the intramural Branches, and several working groups have been formed to help ensure

coordination of activities. These groups are concerned, for example, with the development and utilization of epidemiology data resources and record-linkage systems, as well as with studies of cancer-prone families, diet and nutrition, female cancers, drug-induced cancer, epidemiologic methodology, computer systems, biochemical epidemiology, and emergent issues such as AIDS.

Extramural Programs

The Extramural Programs Branch plans and manages a national extramural program of basic and applied research in cancer epidemiology, biostatistics, genetics, and related multidisciplinary activities. The Branch mainly utilizes the grant mechanism, but contracts and cooperative agreements are also employed when appropriate. The Branch consists of program areas in biometry (including genetics), epidemiology, and the special interest areas of AIDS research, nutrition, tobacco and health, and biochemical epidemiology. Staff members keep abreast of scientific developments in order to identify specific areas of epidemiologic research that needs special attention and support. This year, several initiatives were continued to further stimulate and reorient investigations on the epidemic of AIDS and AIDS-associated neoplasia, utilizing grants and cooperative agreements, plus a contract-based study to investigate the natural history of AIDS in collaboration with the National Institute of Allergy and Infectious Diseases. The biological specimens from this large-scale multi-center study will be important to clarify the relationships between HTLV-III, immunologic abnormalities, and AIDS. The Branch is also supporting investigations of anogenital cancers, which occur excessively in homosexual populations and have appeared to parallel the epidemic of AIDS.

The Branch has attempted, whenever possible, to facilitate multidisciplinary research in cancer etiology. A request for applications (RFA) was issued this year in the area of biochemical epidemiology to enhance the development, validation and application of laboratory procedures in detecting environmental and dietary exposures that might affect cancer risk. Emphasis was also given to studies designed to identify, characterize, and validate markers of present and past dietary exposures that could be useful in the conduct of nutritionally-focused studies in cancer epidemiology and etiology. Because obesity appears related to several cancers in women, an RFA was issued to clarify the associations and the underlying mechanisms. In response to concerns about the possible relationship between passive smoking and lung cancer, an RFA was issued to stimulate work in this area.

A workshop involving NIH staff and extramural epidemiologists was held this year to review existing mechanisms for extramural support of epidemiologic research. The meeting was successful in identifying some problem areas and possible corrective actions. The workshop report with several recommendations was approved by the Division's Board of Scientific Counselors. The Branch also coordinated a congressionally mandated program designed to stimulate small business participation in Federal research and development projects. Toward this end, the Branch worked closely with intramural staff to develop a series of project statements for activities suitable for small business efforts in epidemiology, biostatistics, and related areas.

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

Prospects

It is difficult to project activities over time, given the current restrictions on available positions and funding, and the uncertain direction that new leads and opportunities will take. However, a major E&B objective is to attain a comprehensive, flexible, and balanced program that will enhance our capacity at the national level to generate fresh ideas and help settle key questions in cancer epidemiology and biostatistics. Special emphasis is being given to pursue existing lines of research through in-depth studies and to make the most efficient use of resources located at NCI and several Federal agencies. With the recent reorganization, the responsibility of the Program has been extended to encompass extramural as well as intramural research. Indeed, all E&B staff have a clear obligation to provide biometric and epidemiologic support to various parts of the National Cancer Program, to foster parallel and complementary efforts throughout the Program, and to promote epidemiology training opportunities at NIH and elsewhere. With continuing interest in environmental cancer and in the contribution to etiology and prevention that can be made through the epidemiologic approach, the E&B Program is challenged not only to increase the scope of its work but also to help develop Institute and Federal programs and policy in several areas.

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

More attention will be given to understanding reasons for ethnic differences in cancer risk (e.g., high rates of certain cancers in blacks) and to the study of less common neoplasms, involving collaborative case-control studies

in several areas or centers, often utilizing the network of SEER registries. Throughout the Program, but especially in the Biostatistics Branch, special efforts will be made to ensure that data from epidemiologic studies are utilized for critical evaluation of methodology and development of more efficient approaches, investigation of carcinogenic mechanisms of action, and research into quantitative risk assessment. Although the E&B Program contributes mainly to cancer etiology, the staff has provided support for many other activities at NCI and other agencies, while also benefiting from this collaboration. Epidemiologic and biostatistical approaches permeate a number of NCI programs and are fundamental to the design and evaluation of a wide variety of methods designed to understand and control cancer. Toward this end, the effectiveness of both intramural and extramural initiatives will continue to depend upon our success in promoting interaction and coordination with many other segments of the National Cancer Program.

ANNUAL REPORT OF

THE BIOSTATISTICS BRANCH

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

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

The Biostatistics Branch was reorganized during the year, following the appointment of Dr. William Blot as Branch Chief, to better enable the accomplishment of these functions. The reorganization also helped to further integrate the Branch within the Epidemiology and Biostatistics (E&B) Program and to re-establish a strong and active statistical unit within the Division of Cancer Etiology (DCE). Last year most of the personnel in the Branch (then called the Biometry Branch), including almost all those involved with the administration of the Surveillance, Epidemiology and End Results (SEER) program and research in clinical trials, were transferred from DCE to the Division of Cancer Prevention and Control. Remaining at that time were members of the Mathematical Statistics and Applied Mathematics Section (Dr. John Gart, Chief), the Information Resources Management Section (Mr. J. Michael Stump, Acting Chief), and several staff in the Office of the Chief. Dr. Gart and then Dr. Joseph F. Fraumeni served as Acting Chief of the Biostatistics Branch until Dr. Blot was appointed Branch Chief in November of 1984.

By February 1985 the Epidemiologic Methods Section was created, the Analytical Studies Section was transferred to the Branch from the Environmental Epidemiology Branch (EEB), and the Information Resources Management Section was permanently assigned personnel on temporary detail from the EEB. Dr. Mitchell Gail was named Chief of the Epidemiologic Methods Section, while Dr. Blot continued as Chief of the Analytical Studies Section (his position while this section was within the EEB) and Mr. Stump was appointed Chief of the Information Resources Management Section. Scientific personnel originally in the Office of the Chief were assigned to sections as follows: Dr. Thomas Fears and Dr. Joan Aron to the Epidemiologic Methods Section; Dr. Susan Devesa, Dr. Debra Silverman, and Mr. Joseph Scotto to the Analytical Studies Section; Dr. Jay Lubin was reassigned from the Analytical Studies Section to the Epidemiologic Methods Section.

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

Mathematical Statistics and Applied Mathematics

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

Statistical Research: Activities cover a wide spectrum of topics in mathematical statistics, probability, and applied mathematics. Completed during the year was research on appropriate methods for the statistical analysis of HLA (human leukocyte antigen) data. One published paper provided a test of whether the frequency of double recessives exceeds zero, while another described estimation and homogeneity testing procedures when the sample contained no such double recessives. Work is also ongoing in ABO-like genetic systems on Bernstein's estimators and the associated test of the Hardy-Weinberg law. Research continued on the analysis of frequency data, survival data, heterogeneity tests, and methods for incorporating historical control data in the analysis of proportions, with application to laboratory and carcinogenicity studies of cancer. One major application concerns analyzing survival curves produced by in vitro exposure of cultured cell lines to DNA-damaging agents. Work is also continuing to investigate modelling of tumor growth kinetics and research in the mathematical theory of epidemics.

Research was conducted on several topics in statistical methodology applicable to epidemiologic studies. One paper has given a simple form of the interaction test used in multiply-matched case-control studies. Another gives approximate tests and interval estimation for the common relative risk useful in stratified prospective studies. Statistical methods for comparing several simple harmonic trends in disease incidence and approximate sample size determination for detecting linear trends were examined. An evaluation of the empirical logit transformation and the properties of various transformations of binomial variables has also been conducted. The bias of the maximum likelihood estimator of the common slope in stratified logistic regression was investigated and corrections made for skewness in the analyses of a common relative risk in stratified prospective studies.

Finally, work continued on the development of more efficient methods for obtaining exact results in the combination of 2x2 tables. Dramatic reductions in computer time have been obtained when the number of tables is large and the sample sizes are small and/or the marginal totals of some tables in the set to be combined are identical. These methods are particularly useful in evaluating some improved asymptotic estimators. Work was also done to develop efficient computer algorithms for exact randomization tests in the case of multiple strata analogous to the exact test for trend in binomial data. These methods are especially useful in evaluating the performance of various approximate methods.

Statistical Consulting: During the year the staff advised and collaborated with investigators throughout the Cancer Institute, particularly on statistical methods for laboratory studies. In the Epidemiology and Biostatistics Program, this consultation included the evaluation of data arising from a project to determine the feasibility of using assays for fecal mutagenicity in a proposed case-control study of colorectal cancer; the design and evaluation of studies to determine the prevalence of antibodies to the human T-cell lymphotropic virus (HTLV-I) in at-risk populations, and to identify risk factors associated with HTLV-I infection; statistical methods for the analysis of in vitro cell survival studies; and study of nasopharyngeal carcinoma in Chinese in Singapore evaluating the relation of Epstein-Barr virus antibody levels and HLA profiles to survivorship. Consultation with NCI staff outside the Program was also extensive. Major activities included work on experiments to elucidate the mechanisms of increased cancer susceptibility to induced chromosome damage in fibroblasts from patients with a variety of cancer-prone disorders; the proper statistical evaluation of a long-term study on the carcinogenic effects of radiation on dogs; statistical analysis of rates of conversion of papillomas to carcinomas in mouse skin painting experiments; study of the in vitro survival of lymphoblast and fibroblast cell lines from patients with cancer-prone diseases and with primary neuronal degenerations after exposure to DNA-damaging agents, and the design and statistical analysis of a blind experiment performed to confirm findings of radiosensitivity of these cell lines; statistical analyses to determine the prognostic value of various factors in a clinical trial of testicular cancer; studies of the prognostic value of tumor staging for patients with various types of cancer; and statistical and genetic problems associated with mathematically modelling the steps involved in the conversion of a normal cell to a malignant tumor.

Finally, chapters for an International Agency for Research on Cancer monograph on methods for the statistical analysis of long-term animal carcinogenesis experiments were prepared.

Epidemiologic Methods

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

Several Branch members contributed to the adaptation and development of statistical methods useful in the design and analysis of case-control studies. A general survey paper unified elements of design of case-control and cohort studies, showing that various biases in prospective designs have a direct correspondence in retrospective designs and vice versa. The applicability of the case-control methodology was enhanced by reports that detailed the use of case-control studies when several diseases are simultaneously under study or when disease can recur and provided estimates of population attributable risk with multiple risk factors. A subtle design flaw that can occur in hospital-based case-control studies was described. Problems with the

use of dead controls also were evaluated. Responses from next-of-kin of dead controls were found to differ significantly from those of living controls in several variables, such as cigarette, alcohol, and drug use.

One review summarized problems that can arise from using surrogate interviews and considered other practical issues in the design and conduct of case-control studies. A further study examined the effect of excluding certain causes of death on control exposure rates.

Several reports expanded methodology for use in occupational and other cohort studies. Guidelines for sampling case-control data from a cohort study to obtain unbiased risk estimates were given. For each case incident with the disease of interest, controls must be selected with replacement from all cohort members at risk or without replacement from all non-cases in order to obtain an unbiased estimate of relative hazard. Another report highlighted the importance of examining age and year-specific standardized mortality ratios and the choice of standard population. A demonstration of the use of the standardized mortality or morbidity ratio for detecting excess disease risk in family pedigree data was presented. The report also critiqued a new proposed methodology and found it generally inadequate. Work has continued on the development of, and accessibility to, the E&B computer program library. Statistical Analysis System (SAS) pre-programmed subroutines to estimate and test relative risks and to facilitate conditional regression modeling with matched case-control data were expanded. Procedures for efficient data retrieval from large SAS computer files using direct access were detailed.

Work is in progress to develop new mathematical models of cancer progression. Data from a trial of breast cancer screening are being incorporated into a study of the natural history of breast cancer. Preliminary analyses of patterns of survival suggest that mortality can be reduced among subsets of the breast cancer cases detected in the screening program. Other completed work on the natural history of breast cancer was described in papers on the staging of second primary breast cancer and inflammatory breast cancer.

One member of the Branch is exploring mathematical models of infectious agents and cancer. Papers on the influence of seasonal transmission on cycles of disease incidence and research problems in this general area were also published.

Several staff are involved in problems in the area of quantitative risk assessment, and provide statistical consultation, review, and support to scientists throughout the Cancer Institute and at regulatory agencies. The Branch will continue to develop statistical methodology to deal with various problems in quantitative risk assessment as well as mathematical models of cancer induction and progression. Special emphasis has been placed on critical evaluation of methods for extrapolating from high to low doses.

Analytical Studies

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

Patterns of cancer incidence and mortality: Particular attention is paid to analyses of trends in cancer incidence and mortality. Although the administration of the SEER program was transferred to DCPC last year, the Branch continues to cooperate in the analysis and interpretation of national cancer incidence data. Analysis and manuscript preparation are continuing regarding cancer incidence and mortality trends among whites from the late 1940s to the early 1980s. The studies show that although both the incidence and mortality from stomach cancer have been declining continuously for many years, the rate of decrease may be abating. Incidence declines are also continuing for cancer of the uterine cervix; as yet, there have not been any increases in either invasive or in situ carcinomas of the cervix among young women in this country, which might have been expected from the increasing prevalence of sexually-associated risk factors in the population. Although the age-adjusted incidence and mortality rates for ovarian cancer have changed little during the past 30 years, some decreases are apparent among the younger age groups, whereas increases are reported among the older age groups. The incidence of prostatic cancer has shown continual increases, while mortality rates have remained fairly stable. The Branch also participated in descriptive surveys of cancer incidence trends in Connecticut, from 1935-1939 to 1975-1979. A monograph on the occurrence of second tumors was prepared to help commemorate the 50th anniversary of the nation's oldest cancer registry.

In one descriptive analysis, changes in age-specific national breast cancer mortality rates during 1950-1980 were correlated with changes in childbearing practices in early adulthood, except for the most recent 5-year period among women below age 40. In this age group mortality rates declined in the late 1970s even though a rise was anticipated based on delayed childbearing among this cohort in the 1960s. The decline was even more noteworthy since there was a rise in breast cancer incidence among younger women, and suggested that changes in the management of breast cancer instituted in the mid-1970s may be contributing to the lowered death rates for breast cancer.

Another descriptive study revealed that colorectal cancer incidence and mortality rates for 1975-1979 for Puerto Rican-born residents of New York City were about two times those for Puerto Ricans living in Puerto Rico, but less than those for other whites in New York City, suggesting that changes in lifestyle and environment may be involved in the higher rates in migrants. For stomach cancer, incidence rates for Puerto Rican born residents were slightly, but not significantly, higher than rates for those in Puerto Rico. In contrast, stomach cancer mortality rates for Puerto Rican residents of New York were lower than rates in Puerto Rico throughout the survey period. Trends in national testicular cancer incidence and mortality were also evaluated during the year. An epidemic increase in incidence among young men was observed, but mortality has now begun to decline due to improved treatment of this cancer.

Collaborative Case-Control and Cohort Studies in the United States: The Branch also undertakes collaborative investigations to identify and quantify risk factors for cancer. Interviewing of cancer patients and controls continued in a multi-center population-based case-control study of oral cancer in New Jersey, Atlanta, Los Angeles, and the San Francisco area. The study, which will enroll

nearly 1,500 cases and 1,500 controls, will be the largest of its kind and will enable evaluation of the effects of smokeless tobacco (chewing tobacco and snuff), diet, electronics manufacturing and certain other occupational exposures, and mouthwash use. Interviewing was completed for a case-control study of esophageal cancer in coastal South Carolina. The study was conducted in collaboration with the Medical University of South Carolina, and was initiated to investigate reasons for the high rates of mortality from this tumor first detected in the 1940s. Field work has begun for a case-control study of biliary tract cancer in Los Angeles in collaboration with the University of Southern California. Both bile duct and gallbladder cancer will be studied to provide etiologic clues to these rare malignancies.

A case-control study of testicular cancer in the Washington, D.C., area was completed during the year. Initial analyses showed that undescended testis was the major risk factor. Ongoing analyses are focusing on occupational exposures and pre- and perinatal events in an attempt to determine reasons for the rising incidence of this cancer among young men.

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

The skin cancer investigation included evaluation of incidence patterns, assessment of ultraviolet (UV) light exposures in collaboration with the National Oceanographic and Atmospheric Administration and Temple University, and idenitification of risk factors via a case-control study involving telephone interviews in 12 areas of the country. Annually, about one-half million Americans develop basal cell or squamous cell carcinomas of the skin. Groups of individuals at high risk of developing skin cancer have been identified and relative risk estimates calculated. Host attributes associated with increased risk included a history of moles/birthmarks, acne, psoriasis, warts, and freckles, and persons of English, Scottish or Irish ancestry. Environmental determinants included outdoor exposure to sunlight, place of residence, particularly residence in areas receiving relatively high amounts of UV-B light, and treatment with ionizing radiation, coal tar or pitch, and arsenic.

This year special attention was paid to differences in patterns for melanoma and nonmelanoma skin cancer. Characterization of the anatomic distribution of the two skin cancers revealed striking differences. Over 80% of basal cell and squamous carcinomas of the skin are found in exposed areas of the body, but melanomas predominate on the trunk (45%) in white males and legs (35%) in white females. New correlation studies of the relation between ultraviolet light and

melanoma showed that the relative effects of UV-B were greatest for sun-exposed areas of the body (face, head, neck, upper extremities). Although the degree of association with UV-B was not as strong as for nonmelanoma cancers, the significant positive correlation persisted after adjustment for known risk factors.

Analysis also continued on data collected from a large case-control study of renal cancer in Minneapolis-St. Paul. Research this year focused on drug and occupational exposures. An association was found between renal pelvis cancer and long-term use of phenacetin and acetaminophen-containing analgesics. The link to acetaminophen was based on small numbers of cases, but is of concern in view of a recent report of carcinogenicity in an animal experiment with this commonly used medication. To evaluate further the issue of analgesics and renal pelvis cancer, plans for a large multi-center case-control study are being developed. No strong link to petroleum exposure was detected, although a slight increase in kidney cancer risk was noted among gas station attendants, an intriguing finding in view of reports of kidney cancer in animals exposed experimentally to unleaded gasoline.

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

Another cohort study identified cancer deaths among users of smokeless tobacco among 250,000 U.S. veterans who filled out a tobacco use questionnaire in 1954 or 1957. Preliminary analyses show increased risks for certain oral cancers, including cheek and gum tumors, and for cancers of the small intestine. The Branch also participated in investigations of retroviruses (HTLV-III) in cohorts of homosexual men.

International studies: A major emphasis is the conduct of analytical epidemiologic/biometric studies in areas of the world which offer special opportunities for research on cancer etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high-risk areas 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, few of whom smoke. The Shenyang study will also examine the role of arsenical air pollution from China's largest nonferrous smelter. In total, over 9,000 interviews are being conducted in these investigations which are scheduled for completion beginning next year. A large-scale randomized intervention trial was also initiated in Linxian during the year. One component of the trial focuses on 3,000 persons with esophageal dysplasia, a precursor lesion for esophageal

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

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

In collaboration with the University of Bergen in Norway, cohort analyses of diet and cancer are ongoing. Several cohorts of Norwegians are followed, including a sample of men from the general population, siblings of migrants to the United States, and individuals who participated in case-control studies conducted in the mid-1960s. Using statistical methodology and computer programs developed by the Branch, the Norwegian cohort study has provided clues to risk factors for pancreatic cancer, including cigarette smoking, use of smokeless tobacco (snuff dipping and chewing), and alcohol consumption. No effect of coffee drinking was detected.

Ongoing collaboration with investigators in Sweden on the analysis of linked census and cancer registry data has evaluated occupational factors in the occurrence of pleural mesothelioma, nasal cancer, and other neoplasms. This large national resource, linking data from the 1960 census with cancer incidence data covering the entire Swedish population over the period 1961-1979, is being utilized to generate and test hypotheses regarding occupation and cancer.

To date increased risks of mesothelioma have been found among shipyard and railroad workers, confirming previous reports, and among paper-pulp workers, establishing new hypotheses. Nearly one-quarter of all nasal adenocarcinomas in Swedish males occurred among furniture makers, yet less than 2% of the work force was employed in this occupation. There was also a 2-fold increase of squamous nasal tumors among textile workers. A similar finding was reported this year from a case-control study of nasal cancer conducted in Virginia and North Carolina by Program staff.

A collaborative case-control study of stomach cancer was initiated during the year to investigate reasons for the high risk of this cancer in parts of north and central Italy. Some provinces in this region have among the highest stomach

cancer mortality rates in the world, approaching or exceeding those in Japan. Branch staff are collaborating in the design and conduct of the study which will concentrate on dietary exposures, including the apparently high consumption of preserved meats in the high-risk areas.

Information Resources Management

The Branch is responsible for assuring adequate computer-related support to the epidemiologists and biometricians throughout the E&B Program. Activities involve the administration and monitoring of two computer-support contracts and the assignment of computer analysts to support individual research projects. The major computer-related activities included systems development related to the Flow Automated Cell Sorter (FACS) laboratory at the Uniformed Services Univeristy for Health Sciences; establishment of a microcomputer applications project to increase the utility of this tool for administrative, scientific, and training purposes and to keep the Branch at the forefront of developments in this new technology; the drafting, issuing and monitoring of master order agreements to provide for the tracing of individuals in cohort studies, generation of cancer mortality rate statistics over 1950-1980 for selected geographic areas; and a Program-wide consolidation of contracting activities. Active consulting relationships are also maintained with other NCI groups, including programs in the Office of the Director, the Division of Extramural Activities, and the Division of Cancer Prevention and Control.

Prospects

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

SUMMARY REPORT

BIOSTATISTICS BRANCH

PROGRESS ON RESEARCH CONTRACTS

The Branch's three research contracts ($719,000) support unique or rare opportunities to study populations with unusual risk patterns and exposures in order to understand better the etiology of certain cancers.

One contract has determined cancer incidence among Alaskan natives and has examined trends in both incidence and mortality over time. Striking excesses of certain cancers exist among Alaskan natives. The increased incidence is greatest (15-fold or more compared to rates in U.S. whites and blacks) for nasopharyngeal carcinoma, with increased rates also evident for salivary gland, kidney, liver, and gallbladder cancers. In contrast, the total cancer rates are at or slightly below U.S. norms. The cancer distribution in natives is changing, however, as lung, colorectal, and breast cancers have become the leading cancers in recent years. The contract enables the continued monitoring of cancer and the development of hypotheses to explain the unusual and changing patterns of cancer in this unique population group.

To evaluate risk factors in high cancer risk areas of China, two collaborative contracts were negotiated with the Chinese Academy of Medical Sciences. The first (CP-21012) supports four case-control studies: esophageal cancer in Linxian, where esophageal cancer rates are the highest in the world; lung cancer in Shanghai, where rates are exceptionally high in women even though few smoke; choriocarcinoma in Beijing; and stomach cancer in Shandong province, where unusual opportunities exist to evaluate dietary factors. Research protocols that detailed methods for case ascertainment, control selection, blood and urine collection, and field survey procedures were developed and the studies were begun during the year. Pilot studies had shown that population-based cases and controls can be efficiently identified and selected both in rural and urban areas, that registration systems permit an essentially complete tracing of individuals, and that participation and compliance rates are exceptionally high. The second contract (NO1-CP-41019) enables the conduct of a 5-year randomized intervention trial in Linxian to test whether vitamin/mineral supplementation can lower the incidence of this tumor. During the year the trial was designed, the study population screened for eligibility and donation of sera to be stored, and the first pills issued. In total 33,000 persons were enrolled and monitoring of their cancer experience was begun.

BIOSTATISTICS BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY'85

Institution/Principal Investigator/ Contract Number	Title
Center for Disease Control Ann Lanier Y01-CP-00500	Epidemiologic Studies of Cancer in Alaskan natives.
Chinese Academy of Medical Sciences Li Bing N01-CP-21012	Epidemiologic Studies of Cancer in China.
Chinese Academy of Medical Sciences Li Bing N01-CP-41019	Nutrition Intervention Trial in Linxian China.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04265-20 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Consulting in Statistics and Applied Mathematics

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

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

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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.)*

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

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

The methodology of applied mathematics, mathematical statistics and probability is applied to biomedical problems. Often 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. 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, together with Mr. Scotto of the Analytical Studies Section, continues his collaboration on two large prospective studies on the relationship of diet and cancer being done at the University of Bergen in Norway and at the University of Minnesota. Current work has concentrated on the possible relation of vitamins A and C intake and alcohol consumption to lung cancer in an American cohort. The work is collaborative with Professors Erik Bjelke and Leonard M. Schuman.

Mr. Nam has continued to collaborate with Mr. Scotto of the Analytical Studies Section on a special survey of non-melanoma skin cancer cases in whites in eight U.S. localities with regard to cyclic seasonality in incidence.

Dr. Pettigrew is advising Dr. Mark Schiffman of the Environmental Epidemiology Branch regarding the evaluation of data arising from a project to determine the feasibility of using assays for fecal mutagenicity in a proposed case-control study of fecal mutagenicity and colorectal cancer.

Dr. Tarone advised Dr. Jeffrey Clark and Dr. Edward Murphy of the Environmental Epidemiology Branch regarding the design and evaluation of studies to determine the prevalence of antibodies to the human T-cell leukemia virus (HTLV I) in at-risk populations, and to identify risk factors associated with HTLV I infection.

Dr. Tarone advised Dr. Dilys Parry of the Clinical Epidemiology Branch regarding statistical methods for the analysis of in vitro cell survival studies. Dr. Tarone also advised Dr. Allen Bale and Mr. Frank McKay of the Clinical Epidemiology Branch regarding statistical issues.

Mr. Nam and Dr. Gart have continued to collaborate with Dr. Paul Levine of the Clinical Epidemiology Branch on a study of nasopharyngeal carcinoma (NPC) in Chinese in Singapore with regard to Epstein-Barr virus antibody level and survival as well as a possible relation of the HLA profile with survivorship.

Mr. Nam advised Dr. Watanabe of the Clinical Epidemiology Branch on statistical problems in the analysis of Hodgkin's disease incidence data.

Mr. Thomas advised various staff members on technical aspects of computer programming. Again this year, numerous researchers throughout the world have requested and received copies of the computer software developed and used in this section.

Mrs. Smith did much of the data processing and support work for many of the consulting projects detailed herein.

Dr. Gart continued to serve on the E&B Program Review Group.

Dr. Tarone served on the Technical Evaluation of Proposals Committee of E&B.

Division of Cancer Etiology - Biological Carcinogenesis Program

Dr. Tarone continues to perform statistical analyses of experiments performed by Dr. Katherine Sanford and Mr. Gary Jones of the Laboratory of Cellular and Molecular Biology and Dr. Ram Parshad of the Howard University College of Medicine. These experiments are performed to elucidate the mechanisms of increased susceptibility to induced chromosome damage in fibroblasts from patients with a variety of cancer-prone disorders.

Division of Cancer Etiology - Chemical and Physical Carcinogenesis Program

At the invitation of the Low Level Radiation Effects Branch, Dr. Gart has advised scientists at the Argonne National Laboratory on the proper statistical evaluation of a long-term study on the possible carcinogenic effects of radiation on dogs.

Dr. Tarone advised Dr. Henry Hennings of the Laboratory of Cellular Carcinogenesis and Tumor Promotion on the statistical analysis of rates of conversion of papilomas to carcinomas in mouse skin painting experiments.

Dr. Pettigrew is serving on a Source Evaluation Group to assist Dr. James L. Murray by evaluating proposals for continuing Interagency Agreements with the Department of Energy entitled "Late Effects of Protracted Irradiation in Dogs" and with the Food and Drug Administration entitled "Neoplasia in Beagles After Irradiation During Development".

Division of Cancer Biology and Diagnosis

Dr. Tarone continues his collaboration with Dr. Jay Robbins and Ms. Susanna Barrett of the Dermatology Branch in their experiments to study the in vitro survival of lymphoblast and fibroblast cell lines from patients with cancer-prone diseases and with primary neuronal degenerations after exposure to DNA-damaging agents. Dr. Tarone also assisted with the design of, and performed the statistical analysis of a blind experiment performed by Mr. John Nove and Dr. John Little of the Harvard University Laboratory of Radiobiology to confirm findings of radiosensitivity in the laboratory of Dr. Robbins.

Division of Cancer Treatment

Dr. Tarone assisted Dr. Eddie Reed of the Medicine Branch in statistical analyses to determine the prognostic value of various factors in a clinical trial of testicular cancer.

Division of Cancer Prevention and Control

Dr. Tarone advised Dr. Donald Henson of the Organ Systems Section regarding planned studies of the prognostic value of tumor staging for patients with various types of cancer.

Dr. Tarone advised Dr. Kenneth Chu of the Occupational Cancer Branch regarding statistical and genetic problems associated with mathematically modelling the steps involved in the conversion of a normal cell to a malignant tumor.

Other Activities

Dr. Tarone and Dr. Gart continued collaboration on chapters for an International Agency for Research on Cancer monograph on the statistical analysis of long-term animal carcinogenesis experiments.

Proposed Course:

Several of the projects mentioned in the Major Findings section will continue. In particular, the collaboration with the various projects in epidemiology within the Epidemiology and Biostatistics Program, as well as in the Biological Carcinogenesis Program, the Division of Cancer Biology and Diagnosis, and other areas will be progressing.

Significance to Biomedical Research and the Program of the Institute:

Members of this section are assuming an essential role in much research within the National Cancer Institute. Their activities include not only statistical analysis but also planning of valid experiments.

Publications:

Cameron, T. P., Hickman, R. L., Kornreich, M. R., and Tarone, R. E.: History, survival and growth patterns of B6C3F1 mice and F344 rats in the NCI Carcinogenesis Testing Program. Fund. Appl. Toxicol. (In Press).

Fujino, T., Gottlieb, K., Manchester, D. K., Park, S. S., West, D., Gurtoo, H. L., Tarone, R. E., and Gelboin, H. V.: Monoclonal antibody phenotyping of inter-individual differences in cytochrome P-450 dependent reactions of single and twin human placenta. Cancer Res. 44: 3916-3923, 1984.

Gullino, P. M., Grantham, F. H., Hill, B. M., and Pettigrew, H. M.: Effect of pregnancy and nursing on growth of metastases from N-nitroso-N-methylurea induced mammary carcinoma. JNCI 74: 229-233, 1985.

Leech, R. W., Brumback, R. A., Miller, R. H., Otsuka, F., Tarone, R. E., and Robbins, J. H.: Cockayne syndrome: clinicopathologic and tissue culture studies of affected siblings. J. Neuropath. Exp. Neurol. (In Press).

Otsuka, F., Tarone, R. E., Seguin, L., and Robbins, J. H.: Hypersensitivity to ionizing radiation in cultured cells from Down syndrome patients. J. Neurol. Sci. (In Press).

Parshad, R., Sanford, K. K., Jones, G. M., and Tarone, R. E.: Ataxia telangiectasia heterozygotes detected by chromatid damage following x-irradiation of cells in G_2. Cancer Genet. Cytogenet. 14: 163-168, 1985.

Robbins, J. H., Otsuka, F., Tarone, R. E., Polinsky, R. J., Brumback, R. A., and Nee, L. E.: Parkinson disease and Alzheimer disease: hypersensitivity to X rays in cultured cell lines. Journal of Neurology, Neurosurgery and Psychiatry (In Press).

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

Tarone, R. E., Otsuka, F., and Robbins, J. H.: A sensitive assay for detecting hypersensitivity to ionizing radiation in lymphoblastoid lines from patients with Duchenne muscular dystrophy and primary neuronal degenerations. J. Neurol. Sci. 65: 367-381, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04267-20 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Research in Mathematical Statistics and Applied Mathematics

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

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

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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.)*

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

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

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

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.

Jun-mo Nam and John J. Gart have completed their research on the statistical analysis of human leukocyte antigen (HLA) data in which there are no double blanks. The results have been published in two recent papers. They are also continuing their work in ABO-like genetic systems on Bernstein's estimators and the associated test of the Hardy-Weinberg law.

Robert E. Tarone continues his research on the analysis of frequency data, survival data, and heterogeneity tests. He continues to work on improving his method for incorporating historical control data in the analysis of proportions. He has completed a study of methods for correcting the Cochran-Armitage trend statistic for skewness. He is investigating efficient methods of identifying cancer-prone families. He has extended the theory of heterogeneity tests based on efficient scores to the case of nuisance parameters. He also continues research on methods for analyzing survival curves produced by in vitro exposure of cultured cell lines to DNA-damaging agents.

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

Donald G. Thomas continues to develop more efficient methods for obtaining exact results in the combination of 2x2 tables. Dramatic reductions in computer time have been obtained when the number of tables is large and the sample sizes are small and/or the marginal totals of some tables in the set to be combined are identical. These methods are particularly useful in evaluating some improved asymptotic estimators being developed by John J. Gart. Donald Thomas also continues to develop efficient computer algorithms for exact randomization tests in the case of multiple strata analogous to the exact test for trend in binomial data. These methods are especially useful in evaluating the performance of various approximate methods.

Jun-mo Nam is continuing his investigation of the analysis of HLA data for the detection of haplotype association with disease in case-control studies. He is also working on statistical methods for comparing several simple harmonic trends in disease incidence. An investigation of approximate sample size determination for detecting linear trends is also being done.

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

John J. Gart has continued his research on several topics in statistical methodology. A recently published paper has given a simple form of the interaction test used in multiply-matched case-control studies. An accepted paper gives approximate tests and interval estimation for the common relative risk useful in stratified prospective studies. He also has done recent, published work on the bias and skewness of the analysis of the common odds ratio. Joint work with Hugh Pettigrew and Donald Thomas includes a recently published paper on the empirical logit transformation as well as an additional invited paper of further results on this subject which has been prepared for publication. With Jun-mo Nam he is investigating the bias of the maximum likelihood estimator of the common slope in stratified logistic regression, as well as corrections for skewness in the analyses of a common relative risk in stratified prospective studies.

Significance to Biomedical Research and the Program of the Institute:

The interplay between mathematical theory, data analysis and experimental research is an important element in biomedical research. Many of the "major findings" reported above are new statistical techniques which have or may be

directly applied to data collected by the medical researchers at NCI, particularly in DCE, or other workers in cancer research. Others are mathematical models which may also aid in the planning of subsequent experiments or epidemiologic studies. The opportunity for initiating fundamental research on mathematics and mathematical statistics is essential for enabling members of the section to achieve professional recognition among their peers in their own scientific disciplines. More importantly, the possibility of doing such unconstrained research is a prerequisite for the consulting work of the section to be carried out at the highest professional level.

Proposed Course:

Many of the projects described in the major findings will be continued, e.g., analyses of transformations and loglinear methods, analyses of relative risk in case-control studies and prospective studies, and statistical methods in genetics. In addition, new research initiatives will include the development of new statistical methods and mathematical models in various biomedical problems that come to our attention during the year.

Publications:

Gart, J. J.: Analysis of the common odds ratio: Corrections for bias and skewness. Bull. Int. Stat. Inst. (In Press).

Gart, J. J.: Approximate tests and interval estimation of the common relative risk in the combination of 2x2 tables. Biometrika (In Press).

Gart, J. J.: Report of the Editor of Shorter Communications, 1979-1984. Biometrics 40: 1173, 1984.

Gart, J. J.: Testing for interaction in multiply-matched case-control studies. Biometrika (In Press).

Gart, J. J., and Nam, J.: A score test for the possible presence of recessive alleles in generalized ABO-like genetic systems. Biometrics 40: 887-894, 1984.

Gart, J. J., Pettigrew, H. M., and Thomas, D. G.: The effect of bias, variance estimation, skewness, and kurtosis of the empirical logit on weighted least squares analyses. Biometrika 72: 179-190, 1985.

Nam, J., and Gart, J. J.: The ML estimation and testing of generalized ABO-like data with no observed double recessives. Biometrics (In Press).

Tarone, R. E.: On heterogeneity tests based on efficient scores. Biometrika 72: 91-95, 1985.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04269-14 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Biomedical Computing - Consultation, Research and Development, Service

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

P.I.:	J. Michael Stump	Supervisory Systems Analyst	BB	NCI
Others:	D. J. Grauman	Computer Systems Analyst	BB	NCI
	E. J. Lisiecki	Expert	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 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7	6	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 Information Resources Management Section's mission includes: 1) planning and conducting research and development work to improve methodology in the application of computers and data processing techniques in support of research conducted and coordinated by NCI investigators and their collaborators; 2) serving as the focal point in the Epidemiology and Biostatistics Program for the procurement, management and monitoring of data 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 on ADP and office automation issues, problems and operations.

PROJECT DESCRIPTION

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

J. Michael Stump	Supervisory Systems Analyst	BB NCI
Dan J. Grauman	Computer Systems Analyst	BB NCI
Edwin J. Lisiecki	Expert	BB NCI
Richard I. Ramsbottom	Computer Specialist	BB NCI
Boyd L. Stephenson	Computer Specialist	BB NCI
Ruth S. Wolfson	Computer Programmer/Analyst	BB NCI

Objectives:

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

Methods Employed:

The Information Resources Management Section (IRMS) staff applies management analysis methods, systems analysis techniques and computer programming expertise to the planning, design, development and implementation of information processing systems for scientific projects having data management and statistical computing requirements. This involves evaluating alternatives and making recommendations on the technical feasibility and budgetary implications of various methodological approaches to computing support for individual research projects; participating on technical selection and review committees for grants and contracts; assisting investigators in identifying and obtaining computer-related resources and services; and conducting training programs, seminars and workshops on various aspects of biomedical computing. IRMS staff also administer and monitor the computer support contracts for the Epidemiology and Biostatistics Program.

The Section's activities are focused on the E&B Program's scientific projects and studies, particularly those projects where resulting methodology, technology and data resources can be applied to other E&B Program projects. Members of the Section have also increased consultation to E&B Program investigators on ad hoc special studies.

Major Findings:

1. FACS System at the Uniformed Services University for Health Sciences

The Fluorescence Activated Cell Sorter laboratory project continued to receive technical and operational support from staff of the Section. Activities included 1) implementing management and technical controls to minimize disruptions to the AIDS and HTLV research program; 2) modifying the PDP-11 computer operating system to incorporate technology advances; and 3) enhancing the application software system in order to provide more refined data analyses. The Section is currently planning for the physical move of the laboratory to a new facility and scheduling the implementation of a microcomputer-based acquisition system.

2. E&B Program Microcomputer Application Project

The objective and scope of this project is 1) to provide a facility for evaluating the capabilities of microcomputers and for supporting their application in the E&B Program; 2) to provide a mechanism for accumulating and disseminating technical materials and other data related to technological advances dealing with the use of microcomputers; and 3) to assist the E&B Program investigators by providing a focal point for guidance, consultation and training in the area of microcomputers. The project is made up of the following components:

- Steering Committee - to provide guidance and direction and to facilitate communication with all E&B Program organizations
- Publication Reference Library - to make available sources of information on current topics of interest
- Microcomputer Workstation - to make available a microcomputer hardware and software configuration for use by program personnel
- Consulting and Training - to provide guidance and support for program personnel planning to use the microcomputer as an administrative or as a research tool
- Application Software Evaluation - to evaluate microcomputer software such as text editors, spreadsheets, databases and word processing application packages

3. Cohort Tracing Activities

The Section has responsibility for all tracing activities related to cohort follow-up. An interagency agreement with the Social Security Administration and master agreement orders with contractors specializing in subject tracing methodology are used to determine the vital status of study subjects. Section staff are responsible for drafting and issuing the master agreement orders, monitoring the computerized tracing management system used by the contractors and keeping informed of the status of each tracing activity.

This year a cost-benefit analysis was produced evaluating the various tracing methodologies used by investigators in the Program. The results of the analysis will allow investigators to make more informed decisions in selecting the most appropriate tracing methodology for their particular study cohort.

4. Generation of Cancer Rate Table Statistics

Staff of the Section designed, developed and implemented a system that produces cancer rate statistics using the actual population and mortality data covering the last 30 years. These tables can be used to improve the accuracy of statistics generated by the Monson and March systems since the tables currently being used by these two systems are based on estimated population and mortality figures. An additional feature of the new system is the capability to select and to compute rates for selected geographic areas.

5. Consolidation of Contracting Activities

A major responsibility of the Section is to coordinate the delivery of computer support services obtained under contract to all components of the E&B Program. Section staff members coordinated the consolidation of requests for computer support services from all four intramural branches of the E&B Program and presented the resulting concept to the DCE Board of Scientific Counselors for approval. This approach enabled the Board to review one concept representing all the major proposed computer support expenditures for the Program. Other benefits include 1) coordination of the use of Program staff in the preparation of Requests for Proposals (RFP's) and the subsequent review of proposals; 2) selection of contractors with complementary technical capabilities which can be applied to support the diverse research tasks within the Program; and 3) provision for more efficient management of computer support activities once contracts are awarded. A Section staff member will be named as a project officer on all contracts awarded as a result of the pending procurement actions.

6. Other Consultation

The Section continues to maintain the Computer Software Inventory, a compilation of data management and statistical software used to facilitate the collection, processing, display and reporting of research data. The document is reissued on a semi-annual basis and contains a functional description of each individual routine along with the required computer resources and any noted limitations to its use. Information on a number of statistical routines currently being

converted for use on the IBM microcompter is planned for inclusion in the next issue. In addition to E&B Program staff, the document is being distributed to computer scientists in the Division of Computer Research and Technology, the Division of Cancer Prevention and Control and the Office of the Director, NCI.

The Section staff participated in a number of ad hoc consultations with E&B Program investigators, with administrative and scientific staff from other DCE programs and with program officials from the Division of Extramural Activities. Various data management, file processing and documentation activities were completed in response to requests for technical consultation and support.

Significance to Biomedical Research and the Program of the Institute:

The systematic capture, organization, and display of complex and diverse data are of considerable importance in the planning, conduct, and management of research efforts. As multidisciplinary and collaborative activities increase in scope and complexity, the problems of linking, manipulating, analyzing, and communicating large quantities of data and information become unmanageable without the assistance of computer related technology.

Proposed Course:

Consultation and technical support will continue to be provided to various NCI research activities.

Publications:

None

CONTRACT IN SUPPORT OF THIS PROJECT

Name of Contractor: IMS, Inc. (NCI-CP-41000-53)

Title: Biomedical Computing Support Services

Current Annual Level: $581,364

Man Years: 12

Objectives: This contract provides computer-related research and services for the scientific activities of the Biostatistics Branch. This support includes the analysis of data sets often involving complex statistical analyses, sophisticated data handling techniques, and state-of-the-art graphics production.

Major Contributions: Computer systems, programs and related products are developed by the contractor in response to requests from NCI biostatisticians, epidemiologists and computer professionals. The contractor also operates the remote terminal facility and provides data technician support related to computer applications.

Proposed Course: The need for these services is expected to continue indefinitely due to the fact that the amount of computer support requested exceeds the capacity of the small in-house group of computer professionals available for consultation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04475-08 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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. L. Fears Mathematical Statistician BB NCI

COOPERATING UNITS *(if any)* Interfederal Agency Task Force on Health Effects of Solar Ultraviolet, Environmental Protection Agency(J.Hoffman); National Oceanic Atmosphere Assoc.(G.Cotton); National Aeronautic and Space Adm.(T.Frederick); National Academy of Medical Science (E.Scott); Temple Univ.(S.Urbach); FDA (M.Johnson)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	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.)*

This project provides epidemiologic data and statistical analyses relative to the etiology of skin cancer, including malignant melanoma. In particular, we measure and clarify the association of disease incidence and mortality with nonionizing solar radiation exposure. Through these studies, NCI provides basic research in response to Public Law 95-95 (Amendment to the Clean Air Act of 1977), which is a commitment to the stratospheric ozone protection policy. The need for these data and analyses of potential human risk has existed since we learned about the decomposition of stratospheric ozone by nitrogen oxides and chlorofluoromethanes (CFMs). Most recent reports (Nature, Nov. 1984) indicate that ozone depletion will be more than 16 percent by the mid-21st century. This will lead to increased amounts of solar ultraviolet, specifically UVB (290nm to 320nm), exposure on earth accompanied by increased incidence in disease. We developed new statistical methodology designed to measure the degree of skin cancer (i.e., basal cell and squamous cell carcinoma) risk according to specific constitutional and environmental factors. Age-race-sex specific relative risk estimates were derived for select geographic areas which vary greatly in the degree or intensity of UVB exposure. We found highest relative risks for caucasians who had been treated for moles (5:1), followed by excess risks (of 2:1 to 4:1) for individuals with histories of exposure to radiation (ionizing), coal tar or pitch, arsenic, or those with acne, psoriasis or warts, or those with outdoor jobs. Fair skin complexion, freckling, inability to tan, and Irish/Scottish ancestry were factors also found to be associated with higher risk to skin cancer (about 2:1). Of major concern has been our projection of incidence of cutaneous tumors. In the United States, we estimate an average annual increase of six percent for melanoma, and three percent for skin cancer. Results from our mathematical models indicate that the effect of UVB is significant for each type of skin malignancy, including melanoma, even after adjusting for demographic, constitutional and other environmental factors.

PROJECT DESCRIPTION

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

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

Methods Employed:

It is essential to this project to obtain reliable measurements of the ground level amounts of solar ultraviolet, UVB (290nm-320nm), at select locations within the United States. In order to clarify, edit, update and evaluate data which has already been collected, and, in order to obtain needed previously unavailable data, we are collaborating with the National Oceanic Atmospheric Administration and Temple University through an interagency contract agreement. Relative amounts of UVB energy reaching the earth's surface are being collected at about 20 geographic locations. Twelve of these are skin cancer or skin melanoma population-based survey areas which were included in special NCI studies or NCI's continuing Surveillance, Epidemiology and End Results (SEER) program. The locations span the United States from coast to coast, and include the Hawaiian Islands at 19 degrees north latitude, and Seattle at 47.5 degrees north latitude.

Random samples of patients from registry files, and random sample of households in the general population from telephone exchange numbers (i.e., the random-digit-dialing telephone procedure) were computer-generated and appropriate epidemiological data were obtained by interview. New procedures were developed to strengthen stratified, multiple and logistic weighted regression analyses. Meteorological methods and formulas were utilized to translate raw counts from sunburn units (i.e., median erythema dose, MED) to energy values in terms of mille joules per square centimeter. One MED is equivalent to 33 mj/cm^2. The Census Bureau provided new intercensal population estimates specific for age,

race, sex, and geographic location. Where possible adjustments were made for Hispanic population groups, which are known to be at lower risk to skin cancer. Specific analyses focused on anatomical sites and histologic types.

Major Findings:

Using available solar radiation data we have developed new estimates of the relative amounts of UVB reaching the earth's surface. We calculate over a two-fold difference in solar ultraviolet energy from our northernmost location Seattle, Washington ($95x10^4$) to Albuquerque, New Mexico ($197x10^4$); and about a three-fold difference to our southernmost location, Mauna Loa, Hawaii ($277x10^4$). We do not detect increasing trends in UVB counts, but our data are currently sparse at many geographic locations (some SEER locations have only two years of useful data). As we have found for nomelanoma skin cancer, correlations of UVB measurements and skin melanoma incidence and mortality were also found to be positive and statistically significant. This is important because of worldwide variability in skin melanoma rates. For example, in central and southern Europe, skin melanoma incidence does not reflect a latitudinal (i.e., UVB) gradient comparable to that found for caucasians in the United States.

We have found that skin melanoma incidence is increasing at a rate of about six percent per year. If this rate continues, we may expect a doubling of cases by the year 2000. Mortality is also increasing about three percent per year for males and less for females. While nonmelanoma skin cancer incidence is about 40 times that of skin melanoma incidence, mortality rates were observed to be about one-third those for skin melanoma during the period 1970-79. These cutaneous malignancies are rarely found among Blacks and pigmented racial groups.

Basal cell and squamous cell carcinomas are usually found on exposed areas of the body (over 80%); but skin melanomas predominate on the trunk (45%) in white males, and on the legs (35%) in white females. These findings have confounded the sunlight hypothesis and have suggested to some that factors other than UV play a major role in the etiology of skin melanoma.

Several years ago, we suggested (using results from our mathematical models) that UV may be etiologically involved in different ways as either an initiator or a promoter in the carcinogenic process. Skin cancers are seen to occur late in life, probably from a lifetime cumulative effect of UV exposure; skin melanoma incidence may result from early, short-term, high intensity, intermittent exposures. Today, these hypotheses are being verified by us and by other researchers working independently. Our current investigations into the association of UV and skin melanoma appear to reflect differences in the degree of association by anatomical site. We found that the degree of association is stronger for exposed sites such as faces, head, neck or upper extremities than for trunk and lower extremities. However, using multiple regression analyses, we could not remove the significant effects of UVB radiation. After adjusting for population-based constitutional variables such as prevelance of moles, freckles, fair skin complexion, celtic ancestry, severe sunburn, etc., and other environmental variables such as ionizing radiation exposure, outdoor occupation, outdoor life-style, industrial and chemical exposure, etc., UVB effects were found positive and statistically significant. Our prelminary findings indicate that the effects of UVB on skin melanoma may be less than those for skin cancer but that this may also depend on cell type and age group.

We found that more than half of all skin melanomas were not otherwise specified (NOS) with respect to cell type classification. There are indications that superficial spreading malignant melanomas and lentigo maligna (Hutchinson's freckle) melanoma may account for the greatest increases in incidence during the past decade; however, this may be an artifact due to idiosyncrosies in reporting at various registries.

New data from Kauai, Hawaii are being received from two dermatologists who see and/or treat virtually all skin cancers on that island. Prelminary findings indicate an unusually high incdence of skin cancer among Japanese descendants. This is a rare finding and new etiologic leads will be pursued where possible.

Significance to Biomedical Research and the Program of the Institute:

This project provides a basis for evaluating the potentially harmful health effects of ozone depletion in our biosphere. New leads on the relative importance of host factors and environmental factors other than UVB may substantially contribute to our knowledge of the etiology of skin cancer and melanoma. This information will play a major role in developing guidelines for the regulation of man-made products, e.g., refrigerants, air conditioning coolants, etc., which may inadvertently modify the chemical balance in the upper stratosphere. The new data provide current estimates of the degree of morbidity from skin cancer and melanoma in various parts of the United States and elucidate the need for cancer prevention programs. The dose-response models provide epidemiologic examples of non-ionizing radiation exposure and skin cancer morbidity and mortality which may be compared with those for ionizing radiation and cancer of non-skin sites. Detailed results will provide appropriate benchmark data for use in prevention, detection, intervention, and screening programs.

Proposed Course:

Intensified analyses of current data bases, including patient and general population information, incidence and mortality rates of skin cancer and skin melanoma, and direct measurement of the amounts of solar radiation (UVB) reaching the earth's surface, will continue. Through our participation in an interfederal agency task force studying the effects of UV in our biosphere, future reports to Congress will include our findings on UVB's role in the etiology of skin melanoma.

In collaboration with NOAA, Temple University and other NCI investigators, a new monograph on UVB measurements including time trends for the years 1974 through 1981 at certain locations is planned. This will be accomplished soon after our interfederal agency contract is implemented. In collaboration with the Environmental Protection Agency and National Aeronautics and Space Administration, we hope to differentiate sunlight energy patterns across the United States, and delineate state-of-the-art measurements with respect to UVB and UVA solar ultraviolet reaching the earth's surface. Estimates of the amount of nonionizing radiation will be calculated for at least one location within each state in the United States. Appropriate correlations of UV exposure and disease risk will be made, emphasizing differences by cell type, anatomical site, sex, age, and race. Seasonal trends and cyclic patterns will also be investigated.

In collaboration with researchers at George Washington University, evaluation will be made of an hypothesis which suggests that certain natural elements on the human skin are photosensitive and may play a role in the immunosuppression system, and in particular with melanocytic cell proliferation. New in-house basic research including case/control studies of skin melanoma and the implications of fluorescent lighting exposure are planned in collaboration with other NCI researchers. In addition further work will be done in collaboration with dermatologists from Kauai, Hawaii, especially in the area of follow-up and case-control studies. We will consult and collaborate with investigators from George Washington University and New York University regarding time trends and lifetime probabilities of developing skin melanoma.

Finally, we will consult and collaborate with Food and Drug Administration investigators who are especially concerned about guidelines for protection from fluorescent lighting exposures.

Publications:

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

Scotto, J.: Melanoma among Caucasians in the United States - Increases predicted for the 1980's. The Skin Cancer Foundation Journal. (In Press)

Kraemer, K. H., Lee, M. M., and Scotto, J.: DNA repair protects against cutaneous and internal neoplasia: Evidence from studies of XP. Carcinogenesis 5: 511-514, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04500-08 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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. Gail	Chief, EMS	BB	NCI
Others:	J. Lubin	Health Statistician	BB	NCI
	W. Blot	Chief	BB	NCI
	L. Pickle	Health Statistician	EEB	NCI
	P. Hartge	Epidemiologist	EEB	NCI
	J. McLaughlin	Staff Fellow	BB	NCI
	D. Silverman	Epidemiologist	BB	NCI

COOPERATING UNITS *(if any)*

Harvard University (J. Robins); Instituto Scientifico Tumori (P. Bruzzi); ORI, Inc. (N. Howard, S. Kalyandrug); Westat, Inc. (J. Cahill)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	

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 develop, adapt, expand and evaluate methodological procedures useful in epidemiologic studies of cancer. Methods of design of case-control studies were given particular emphasis this year, attention focusing on procedures for selecting an unbiased sample from cohort data, selecting controls using random digit dialing, and developing formulae for sample size when exposure is continuous. Prospective and retrospective designs were described within a unified framework based on the proportional hazards model. Adaptations were made to include multiple disase types and recurrent disease, and to estimate population attributable risk with multiple risk factors in case-control studies. Methods for collecting and evaluating dietary data were evaluated. Other work focused on evaluating surrogate responses and assessing quality of response for next-of-kin of dead controls in case-control interview studies. Investigation of general epidemiologic techniques for studying environmental cancer continued.

PROJECT DESCRIPTION

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

M. Gail	Chief, EMS	BB	NCI
J. H. Lubin	Health Statistician	BB	NCI
W. J. Blot	Chief	BB	NCI
L. W. Pickle	Health Statistician	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
J. K. McLaughlin	Staff Fellow	BB	NCI
D. Silverman	Epidemiologist	BB	NCI
D. Byar	Chief, Biometry Branch	DCPC	NCI
A. Hartman	Epidemiologist	DCPC	NCI
T. Fears	Mathematical Statistician	BB	NCI
J. Aron	Staff Fellow	BB	NCI
S. Bale	Staff Fellow	EEB	NCI
L. Brinton	Acting Chief, ESS	EEB	NCI
C. Schairer	Epidemiologist	EEB	NCI
R. Hoover	Chief	EEB	NCI

Objectives:

To develop, adapt, expand, and evaluate methodological procedures useful in epidemiologic studies of cancer.

Methods Employed:

Basic research is undertaken on methodologic techniques which are useful in a variety of epidemiologic settings. Computational algorithms are developed as necessary, and the methods are applied to epidemiologic data generated and collected by investigators in the Biostatistics Branch, the Environmental Epidemiology Branch and elsewhere.

Major Findings:

Several Branch members contributed to the adaptation and development of statistical methods useful in epidemiologic studies. Research continued on methods of design and analysis of case-control studies. A general survey paper unified elements of design of epidemiologic studies, showing that various biases in prospective designs have a direct correspondence in retrospective designs and vice versa. Random digit dialing was studied as an alternative to other population sampling methods, while computer-assisted telephone interviewing has been used

and evaluated. A subtle design flaw that can occur in hospital-based case-control studies was described. One report developed formulae for determining the sample size for a case-control study in which exposure is continuous, thus leading to substantial reductions, compared to dichotomizing exposure, in the required number of subjects. The applicability of the case-control methodology was enhanced by reports that detailed the use of case-control data when several diseases are simultaneously under study or when disease can recur, and for estimating population attributable risk with multiple risk factors.

Problems with the use of dead controls were evaluated. Responses from next-of-kin of dead controls were found to differ significantly from those of living controls in several variables, such as cigarette, alcohol, and drug use. One review summarized problems that can arise from using surrogate interviews and considered other practical issues in the design and conduct of case-control studies. A further study examined the effect of excluding certain causes of death on control exposure rates.

Several reports expanded methodology for use in occupational and other cohort studies. Guidelines for the procedure of sampling case-control data from a cohort study to obtain unbiased risk estimates were given. For each case incident with the disease of interest, controls must be selected with replacement from all cohort members at risk or without replacement from all noncases in order to obtain an unbiased estimate of relative hazard. Another report highlighted the importance of examining age and year specific standardized mortality ratios and the choice of standard population.

Work has continued on the development of, and accessibility to, the E&B computer program library. Statistical Analysis System (SAS) pre-programmed subroutines to estimate and test relative risks and to facilitate conditional regression modelling with matched case-control data were expanded. Procedures for efficient data retrieval from large SAS computer files using direct access were detailed.

Issues surrounding the use of food frequency questions to assess dietary intake were addressed in two reports. One assessment showed that total vitamin A intake is well predicted by intake of few selected dietary items. Another critiqued the calculation of odds ratios using a surrogate measure of intake. These reports impact the design of future dietary questionnaires by demonstrating that the researcher need only concentrate on a few indicator food items in order to characterize diet.

A detailed description of the methodology used in the disease mortality rates for generating cancer atlases and for assessing trends over time was given. One review paper highlighted time-related events in descriptive, case-control, cohort, and experimental studies and their informativeness in providing clues to etiology.

A demonstration of the use of the standardized mortality or morbidity ratio for detecting excess disease risk in family pedigree data was presented. The report also critiqued a new proposed methodology and found it generally inadequate.

Work is in progress to develop new mathematical models of cancer progression. Data from a trial of breast cancer screening are being incorporated into a study of the natural history of breast cancer. Preliminary analyses of patterns of survival suggest that mortality can be reduced among subsets of the breast cancer cases detected in the screening program. Other completed work in breast cancer history was described in papers on stage of second primary breast cancer and inflammatory breast cancer.

One staff member is exploring mathematical models of infectious agents and cancer. Papers on the influence of seasonal transmission on cycles of disease incidence and research problems in this general area were also published.

Several staff are involved in problems in the area of quantitative risk assessment, and provide statistical consultation, review, and support to scientists at the National Cancer Institute and at regulatory agencies. Research will continue to develop statistical methodology to deal with various problems in quantitative risk assessment as well as mathematical models of cancer induction and progression. Special emphasis has been placed on critical evaluation of methods for extrapolating from high to low doses.

Significance to Biomedical Research and the Program of the Institute:

Research in statistical and epidemiologic methodology will help provide means for adequate analyses of the epidemiologic studies carried on by members of the Branch, as well as by epidemiologists in other institutions.

Proposed Course:

Methods development and adaptation will continue, with particular emphasis on techniques applicable to the Branch's analytical epidemiologic studies program.

Publications:

Aron, J. L., and Prorok, P. C.: An analysis of the mortality effect in a breast cancer screening study. Int. J. Epidemiol. (In Press).

Aron, J. L., and Schwartz, I. B.: Seasonality and period-doubling bifurcations in an epidemic model. J. Theor. Biol. 110: 665-679, 1984.

Aron, J. L., and Schwartz, I. B.: Some new directions for research in epidemic models. IMA J. Math. Appl. Med. Biol. 1: 267-276, 1984.

Blot, W. J.: Practical issues in the design and analysis of case-control studies of cancer. In Hirayama, T. and Blot, W. J. (Eds): Biostatistical Methods in Cancer Epidemiology. Hiroshima, Japan, Radiation Effects Research Foundation. (In Press).

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

Bruzzi, P., Green, S. B., Byar, D. P., Brinton, L. A. and Schairer, C.: Estimating the population attributable risk for multiple risk factors using case-control data. Am. J. Epidemiol. (In Press).

Gail, M. H., Lubin, J. H., and Silverman, D. T.: Elements of design in epidemiologic studies. In C. Delisi and J. Eisenfeld (Eds.): Mathematics and Computers in Biomedical Application. North Holland, Elsevier Science Publishers, 1985, pp. 313-323.

Hartge, P., Brinton, L. A., Rosenthal, J., Cahill, J., Hoover, R. N., and Waksberg, J.: Random digit dialing in selecting a population-based control group. Am. J. Epidemiol. 120: 825-833, 1984.

Howard, N. and Pickle, L. W.: Efficient data retrieval: direct access using the POINT option. In Proceedings of the Ninth Annual Conference of the SAS Users Group International. Cary, North Carolina, SAS Institute, Inc., 1984, pp. 294-298.

Kalyandrug, S. and Lubin, J. H.: PROC PECAN - a SAS procedure. In Proceedings of the Tenth SAS User's Group International, Reno, Nevada. Cary, North Carolina, SAS Institute (In Press).

Lubin, J. H.: Case-control methods in the presence of multiple failure times and competing risks. Biometrics (In Press).

Lubin, J. H.: The extension of analytic methods for case-control within cohort studies. J. Chronic Dis. (In Press).

Lubin J. H. and Bale, S. J.: On the detection of excess disease risk in family data. Gen. Epidemiol. (In Press).

Lubin, J. H., Gail, M. H. and Ershow, A. G.: Determining sample size for case-control studies when exposures are continuous. J. Chronic Dis. (In Press).

Lubin, J. and Hartge, P.: Excluding controls: misapplications in case-control studies. Am. J. Epidemiol. 120: 791-793, 1984.

Lubin, J. H., and Lawler, A.: Strateum specific patterns of SMRs and the effects of choice of standard population. J. Occup. Med. (In Press).

McLaughlin, J. K., Blot, W. J., Mehl, E. S. and Mandel, J. S.: Problems in the use of dead controls in case-control studies. I. General results. Am. J. Epidemiol. (In Press).

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

Pickle, L. W.: Re: A comparison of frequency and quantitations methods for epidemiologic studies of diet and disease. (Letter to Editor). Am. J. Epidemiol. 121: 776-778, 1985.

Pickle, L. W. and Hartman, A. H.: Indicator foods for Vitamin A assessment. Nutr. Cancer. (In Press).

Pickle, L. W. and Mason, T. J.: Mapping cancer mortality in the United States. In I. Thornton (Ed.): Proceedings of the First International Symposium on Biochemistry and Health. London, Imperial College. (In Press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04779-09 BB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Field Studies in High Risk Areas

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

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

COOPERATING UNITS *(if any)* Univ.of Minnesota (L.Schuman); Louisiana State Univ.(P.Correa); Univ.of Texas (P.Buffler); Medical Univ.of South Carolina (S.Schuman); Chinese Academy of Medical Sciences (B.Li); Shanghai Cancer Inst.(Y.Gao); Center for Preventive Medicine (E.Buiatti); New Jersey Medical School (C.Yang); USC (B.Henderson)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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 kidney cancer in Minnesota, where ethnic factors, cigarette smoking, and (among women) high relative weight were associated with renal adenocarcinoma, and where cigarette smoking and long-term intake of certain analgesics were found to be risk factors for renal pelvis cancer. Interviewing was completed for case-control studies of respiratory cancer in New Jersey and coastal Texas; lung, stomach, and pancreas cancers in Louisiana; bladder cancer in rural New England; and esophageal cancer in coastal South Carolina. Data are currently being prepared for analysis, but initial results of the lung cancer investigations reveal elevated risks among several occupational groups, including shipyard workers in New Jersey and construction workers in Louisiana and Texas. Smoking of hand-rolled cigarettes was linked to the exceptionally high risk of lung cancer among Cajuns in southern Louisiana. Several new studies were begun this year overseas. Case-control studies of cancers of the esophagus, stomach, and lung and choriocarcinoma were begun in areas of China at high risk of these cancers, while a case-control study of gastric cancer was initiated in areas of Italy that are among the world's highest rates of this malignancy. Also begun was a randomized intervention trial in Linxian, China, where up to one in four persons dies of esophageal cancer, to assess the role of vitamin/mineral supplementation on reducing this extraordinarily high cancer risk. The international studies take advantage of unique opportunities to evaluate diet and other factors, including air pollution, in the etiology of cancer.

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

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

Major Findings:

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

Bladder cancer is the focus of a study begun in rural New England to evaluate the unusually high rates in both sexes in this area of the country. Preliminary analyses indicate that occupational factors are partly responsible, since elevated relative risks were associated with work in the textile and leather industries, two of the area's major employers. In addition, a significant increased bladder cancer risk was found among truck drivers, confirming a relation previously described in a national study of this tumor conducted by the Program.

A correlation study, previously published by the Branch, revealed that nasal cancer mortality was high in counties with furniture manufacturing industries. Subsequent examinations of death certificates from North Carolina, where the industry is most heavily concentrated, showed a four-fold excess of this tumor associated with individuals for whom furniture manufacturing was listed on the certificate as the usual occupation. This year a case-control interview study of cases diagnosed in Virginia and North Carolina over the past ten years was completed. A five-fold excess of nasal adenocarcinoma was found to be associated with wood-working occupations, and a two-fold excess of all tumor types combined found among female textile workers. For the first time, cigarette smoking was shown to be related to nasal cancer, but only to squamous cell types. (See also Project Z01CP04501-08 EEB.) In addition, analyses of linked cancer and census occupational data from Sweden likewise showed a large excess (18-fold) of nasal adenocarcinoma among furniture workers and a 2-fold excess of squamous cancer among textile workers.

A case-control study of cancer of the mouth and throat in North Carolina showed that long-term use of snuff was responsible for the sharply elevated mortality from this cancer among southern women. Additional analyses indicated that increased risks may also be linked to mouthwash use among nonsmokers, to certain

occupations in the electronics industry, and to decreasing consumption of fruits and vegetables. This year a large case-control study of oral cancer (1200 cases, 1200 controls) was begun in Atlanta, New Jersey, Los Angeles, and the San Francisco area to evaluate these associations further. Study of esophageal cancer and diet also continued among blacks in coastal South Carolina, where rates have been high at least since the 1940s.

Renal cancer mortality and incidence rates are high in the north central part of the U.S. An interview study involving 590 cases of renal cancer and 1,180 controls indicates that the area's high rates of renal adenocarcinoma appear to be related at least in part to ethnic factors, as increased risks were associated with German and Scandinavian background, the major ethnic groups in this metropolitan center. One of the strongest risk factors was high weight-for-height, but only among women. Cigarette smoking was associated with about a 60% increased risk of renal adenocarcinoma in men and a 90% increase in women. Separate analysis showed that the relative risk for smoking exceeded five-fold in both sexes for transitional cell cancers of the renal pelvis. Long-term analgesic use was also associated with excess risk of renal pelvis cancer and, to a lesser extent, renal adenocarcinoma. A clue to occupational factors was provided by the increased risk associated among gas station attendants. Although not statistically significant, the finding is of interest since gasoline has induced renal tumors in animal experiments.

Assessment of cancer patterns among Alaskan natives continued, with emphasis on evaluating time trends in both cancer incidence and mortality as the native population adopts a more "western" life style.

A major emphasis has concerned the conduct of analytical epidemiologic/biometric studies in areas of the world which offer special opportunities for research on cancer etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high risk areas in China. These include studying esophageal cancer in Linxian, with the world's highest rates of this cancer; stomach cancer in Shandong Province, where salt consumption is high and where certain foods are regularly eaten that are uncommon elsewhere in China; choriocarcinoma in Beijing; and lung cancer in Shanghai and in Shenyang, to evaluate reasons for the high rates of lung tumors in Chinese women, few of whom smoke. The Shenyang study will also examine the role of arsenical air pollution from China's largest nonferrous smelter. In total, over 9,000 interviews are being conducted in these investigations, which are scheduled for completion beginning next year. A large-scale randomized intervention trial was also initiated in Linxian during the year. One component of the trial focuses on 3,000 persons with esophageal dysplasia, a precursor lesion for esophageal cancer. Another involves 30,000 villagers from the general high risk population. Participants are randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 5-year period. A two group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated 8 group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. The studies will evaluate whether certain groups of vitamins and minerals can inhibit late stage progression to cancer in a high risk population with multiple micronutrient deficiencies, and may have considerable implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

A case-control study of invasive and in situ cervical cancer was conducted in Panama to attempt to explain the high rates of this disease in the country. Interviews, as well as sera, were obtained from 156 of 169 surviving patients and from 309 age-matched neighborhood controls. Although sexual promiscuity was uncommon, it exerted a major effect, with those reporting four or more partners being at a four-fold excess risk. Early first intercourse was common, but it failed to alter risk once number of partners was taken into account. Oral contraceptive use was associated with a two-fold excess risk, which was not substantially affected by control for a variety of sexual parameters. Assays for herpesvirus type 2 showed no relationship to risk with a neutralization test, but a 60% excess risk for those with positive results according to radioimmunoassay. Also begun was a multi-center study in Latin America to investigate reasons for the high rates of invasive cervical cancer. Interviews with women will focus on sexual history, reproductive factors, contraceptive behavior, medical history, and diet. Husbands of women who report only one sexual partner will be interviewed in order to evaluate the role of a "male factor" in the etiology of cervical neoplasia. (See also Z01CP04501-08 EEB.)

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

Significance to Biomedical Research and the Program of the Institute:

These studies allow the testing of hypotheses regarding the etiology of cancer. Answers obtained may lead to the recognition of cancer hazards and may directly suggest actions that need to be taken to prevent the exceptional rates of cancer occurrence in the high-risk areas.

Proposed Course:

Field studies in areas where cancer rates are high will continue. Analysis of the information collected in South Carolina, Louisiana, Texas, and rural New England will be conducted to evaluate reasons for the high cancer rates in these areas. Results from these ongoing studies will help suggest where further epidemiologic research will be worthwhile.

Increased emphasis will be placed on taking advantage of unique opportunities for etiologic study in high-risk areas overseas. Case-control studies of lung, stomach, esophageal, and choriocarcinoma in China will continue, with additional investigations of lung cancer and pollution and of the cervical cancer-penile cancer relationship planned. The case-control studies of gastric cancer in several areas of Italy and cervical cancer in South America will also continue. Initial contacts have been made to explore opportunities for the study of renal pelvis cancer in parts of the Balkan countries where this tumor is the leading cause of cancer death.

Publications

Blot, W. J.: Lung cancer and occupational exposures. In Mizell, M. and Correa, P. (Eds.): Lung Cancer: Causes and Prevention. Verlag Chemie, Deerfield Beach, Fl., 1984, pp. 47-63.

Blot, W. J. and Li, J. Y.: Some considerations in the design of a nutrition intervention trial in Linxian China. Natl. Cancer Inst. Monogr. (In Press).

Brown, L. M., Pottern, L. M., and Blot, W. J.: Lung cancer in relation to environmental pollutants emitted from industrial sources. Environ. Res. 34: 250-261, 1984.

Buffler, P. A., Pickle, L. W., Mason, T. J. and Contant, C.: The causes of lung cancer in Texas. In Misell, M. and Correa, P. (Eds.): Lung Cancer: Causes and Prevention. Verlag Chemie, Deerfield Beach, Fl., 1984, pp. 83-100.

Correa, P., Pickle, L. W., Fontham, E. T. H., Dalager, N., Lin, Y., Haenszel, W. and Johnson, W. D.: The causes of lung cancer in Louisiana. In Mizell, M. and Correa, M. (Eds.): Lung Cancer: Causes and Prevention. Verlag Chemie, Deerfield Beach, Fl., 1984, pp. 73-82.

Ershow, A. G., Zheng, S., Li, G., Li, J., Yang, C., and Blot, W. J.: Compliance and nutritional status during feasibility study for an intervention trial in China. JNCI 73: 1477-1482, 1984.

Gao, Y. T., Blot, W. J. and Fraumeni, J. F., Jr.: A case-control study of lung cancer in Shanghai. Natl. Cancer Inst. Monogr. (In Press).

Hoar, S. K. and Hoover, R.: Truck driving and bladder cancer mortality in rural New England. JNCI; 74: 771-774, 1985.

Li, J. Y., Chen, Z. J., Ershow, A. and Blot, W. J.: A case-control study of esophageal cancer in Linxian. Natl. Cancer Inst. Monogr. (In Press).

Li, J. Y., Li, G. Y., Zheng, F., Liu, Y. Y., Li, P., Yang, C. S., Blot, W. J., Ershow, A. G., Li, F. P., Greenwald, P. and Fraumeni, J. F., Jr.: A pilot vitamin intervention trial in Linxian. Natl. Cancer Inst. Monogr. (In Press).

Mclaughlin, J. K., Blot, W. J., Mehl, E. S. and Fraumeni, J. F., Jr.: Relation of analgesic use to renal cancers: population-based findings. Natl. Cancer Inst. Monogr. (In Press).

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

Wang, T. G., You, W. C., Henderson, B. E. and Blot, W. J.: A case-control study of stomach cancer in Shangdong province. Natl. Cancer Inst. Monogr. (In Press).

Winn, D. M.: Chewing tobacco and snuff. An association with human cancer. In ONeill, I.K. et. al. (Eds.): N-Nitroso compounds. International Agency for Research on Cancer Scientific Publ. No. 57. New York, Oxford Univ. Press, 1984, pp. 837-849.

Wu, P. C., Brinton, L. E., Wang, W., Sung, H. C., Ershow, A., Li, J. Y. and Blot, W. J.: A case-control study of choriocarcinoma in the People's Republic of China. Natl. Cancer Inst. Monogr. (In Press).

Yang, C. S., Sun, S., Yang, Q., Miller, K. W., Li, G., Zheng, S., Ershow, A. G., Blot, W. J., and Li, J.: Vitamin A and other deficiencies in Linxian, a high esophageal cancer incidence area in northern China. JNCI 73: 1449-1454, 1984.

Yang, C. S., Sun, S., Yang, Q., Miller, K. W., Li, G., Zheng, S., Ershow, A. G., Li, J. and Blot, W. J.: Nutritional status of the high esophageal cancer risk population in Linxian, China: Effects of vitamin supplementation. Natl. Cancer Inst. Monogr. (In Press).

CONTRACTS IN SUPPORT OF THIS PROJECT:

WESTAT, INC. (NO1-CP-01044)

Title: Support Services for Epidemiologic Studies

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

Man Years: 45

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

Major Contributions: Analyses were completed for data collected in field studies for oral cancer in North Carolina and renal cancer in Minnesota. Interviewing and/or computational support were conducted for studies of bladder cancer in New England, nasal cancer in North Carolina and Virginia, and esophageal cancer in South Carolina. Forms design and field survey management training were provided for studies of chorio-carcinoma and cancers of the lung, stomach, and esophagus in China.

Proposed Course: Support for a variety of epidemiologic investigations will continue as needed to enable the E&B Program to answer critical questions about the environmental and host determinants of cancer.

CONTRACTS IN SUPPORT OF THIS PROJECT:

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

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

Current Annual Level: $580,241

Man Years: 16

Objective: To provide technical, managerial, and computer support for an epidemiologic study of oral and pharyngeal cancer in 4 areas of the United States.

Major Contribution: Study development and forms design were completed. Currently field work on subject identification and interviewing is underway, and data coding, keying, and editing are in progress.

Proposed Course: Complete case and control ascertainment, medical abstracting, interviewing, coding, keying, and data editing.

ANNUAL REPORT OF

THE CLINICAL EPIDEMIOLOGY BRANCH

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

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

OFFICE OF THE CHIEF

Demography

During the year our computer specialist, Mr. F. W. McKay, has worked toward completion of a population base for studies of cancer mortality, 1950-1981, by county, state, State Economic Area (SEA), Economic Subregions (ESR), and Standard Metropolitan Statistical Areas. Dr. R. Tarone of the Biostatistics Branch has agreed to assist in analyzing the data over time for the various geographic groupings with respect to the influence of different standard populations on adjustment of the data by age.

A system has been written to display ESRs in color on the IBM PC, and has been used to develop mortality profiles for the 119 ESRs. The system can also be used to display profiles for 21 age-groups, and for deaths due not only to cancer but also to circulatory diseases, accidents, and other causes. Dr. Byrne and Ms. Madigan are assisting in further development of the system and in interpreting the results.

A system has been written to examine mortality data at the ESR level using standardized proportional mortality ratios, 1969-1978. Throughout this 10-year interval the National Center for Health Statistics (NCHS) used the eighth revision of the ICD in coding death-certificate diagnoses. NCHS is interested in using data by states to identify health departments whose coding practices are below standard as indicated by the proportion of diagnoses coded as unknown, other or undefined (i.e., with a 9 in the terminal digit). The results should help NCHS improve the accuracy of death certificates by concentrating its educational effort on states that need it the most.

A copy of tapes that list multiple causes of death in 1980 is being obtained. Dr. Mulvihill will assist in posing questions based on his knowledge of the genetics of human cancer; e.g., how does the array of causes associated with neurofibromatosis compare with that for the general population?

Consideration is being given to requests from outside that we update Monograph 22 (mortality by state) and Appendix 1 of Monograph 58 (annual tumor mortality by ICD).

Virus Studies

Liver Cancer and Hepatitis in Veterans of World War II: In the first part of this study, serum specimens for certain hepatitis antigens and antibodies were obtained from about 500 veterans who developed hepatitis in 1942 after immunization with the Rockefeller yellow fever vaccine, received contaminated vaccine without becoming overtly ill, or received no Rockefeller vaccine. There is now sufficient evidence to indicate that the virus was hepatitis B, which is thought to increase the risk of hepatocellular carcinoma.

There are three comparison groups: men with clinical hepatitis, others who received the Rockefeller vaccine which contained the virus but were not ill, and controls who did not receive the Rockefeller vaccine. The studies were done blind with regard to overt disease vs. carrier vs. control, and the code has not yet been broken. A report of the findings will probably be given at a major meeting in the Fall of 1985.

The second component, a cohort study of mortality among the three groups, is progressing well. Death certificates for 14,278 men have been received and coded. For all cases with diagnoses of liver cancer, hospital records will be obtained to verify the diagnoses and eliminate invalid cases.

The third component, a study of liver cancer cases from VA hospitals vs. matched controls, will be studied to determine if the contaminated vaccine was more often received by the men with primary liver cancer. Dr. Beebe is the Project Officer.

Concurrent Clusters of NPC and BL in Texas: In a three-county area of Texas three cases of nasopharyngeal carcinoma (NPC) and three of Burkitt's lymphoma (BL) occurred in less than a year. A search for EBV infection as a feature in common was inconclusive. In the publication, Boss, L. et al. (JAMA 253:2843-2846,1985) urged their readers to study such clusters in the future as thoroughly as possible for a carcinogen, and to store specimens for use when new techniques become available. Dr. Levine collaborated with the Centers for Disease Control in this study.

HTLV in Africa: Higher frequencies of HTLV-I and III were found in Uganda than in the rest of Africa. An intermediate rate of infection was found in Ghana. The sera used for the study were from CEB's Burkitt-Tumor Project. The frequency of HTLV-III, 67% in sera from Uganda collected before 1973, is evidence that Africa is the source of this virus, which is the probable etiologic agent of AIDS (Saxinger, W. C. et al. Science 225:1473-1476, 1984; ibid 227:1036-1038, 1985). The infection in Africa may be asymptomatic, may involve less pathogenic strains than those that induce AIDS, and/or may encounter resistance in populations that have long been exposed. Another possibility is that the infection is less pathogenic when it is transmitted by intravenous or homosexual inoculation. The work was done by Dr. Levine of CEB in collaboration with others at NCI as well as investigators at eight institutions in six countries.

Radiation Studies

Prenatal Effects of Ionizing Radiation: A series of meetings of a Committee on the Prenatal Effects of Ionizing Radiation, chaired by Dr. Miller and sponsored by the National Council on Radiation Protection and Measurements, dealt with two key questions: (a) the induction of cancer by diagnostic exposures in utero, and (b) the implication of a report by Otake and Schull (Brit. J. Radiol. 57:409-414, 1984) that the doubling dose for severe mental retardation was only one rad. The meetings revealed that a normal child is not made mentally abnormal by this low dose, but a shift of the distribution of IQ scores to the left by exposure to ionizing radiation increases the number of children who fall from just above, to just below the borderline for severe mental retardation. Also, some adjustment in the estimate of the doubling dose may be forthcoming when Otake and Schull complete their analysis of grammar school IQ test-scores in relation to radiation dose.

As a result of the Committee's deliberations, a series of suggestions was made to the Radiation Effects Research Foundation concerning the in utero exposed group of Japanese which is nearing 40 years of age. These studies would measure the effects of radiation on the intellect, brain and chromosomes as well as the occurrence of cancer decades after radiation exposure.

Radioepidemiological Tables: The immense task of creating radioepidemiology tables has been completed by the NIH Working Group of which Dr. Beebe was a leading member. The tables give the probabilities that a particular form of cancer was due to a prior exposure to radiation. Time must still be spent, however, in making presentations concerning the tables, preparing testimony for Congress and answering questions related to individual cancer cases.

Other Radiation Activities: The National Council on Radiation Protection and Measurements finished a comprehensive evaluation of the comparative carcinogenicity of ionizing radiation and chemicals. Dr. Beebe prepared the section on the effects of radiation on humans.

Dr. Beebe attends the monthly meetings of the Office of Science and Technology Policy (OSTP) Committee on Interagency Radiation Research and Policy Coordination Science Panel, which has recently dealt with his specialty in considering the Radioepidemiological Tables and an NIH report on a VA proposal to study veterans exposed to atomic fallout. He participates in the regular meetings of the Radiation Epidemiology Branch (REB), NCI, and helps monitor the huge contract that the Low-Level Radiation Effects Branch DCE, NCI, has with the University of Utah for studies of the occurrence of cancer among people in southern Utah who were exposed to fallout from nuclear weapons tests in Nevada in the 1950s. [See below, under Clinical Genetics Section, Laboratory Studies, for a description of research into inherent susceptibility to radiogenic cancer, with respect to female breast cancer after A-bomb exposures under age 20 years, and thyroid cancer after radiotherapy of Israeli children for tinea capitis.]

Mesothelioma

Dr. Beebe is the Project Officer for a contract with the Social Security Administration (SSA) to evaluate the comparability of its employment histories and those already obtained from the next-of-kin of persons who died of mesothelioma.

Some problems are being encountered with regard to disclosure of information from the SSA files. The study is being done in collaboration with Dr. Spirtas of the Environmental Epidemiology Branch (EEB).

A report on a recent increase in the incidence of mesothelioma, as indicated by data from the SEER Program, was given at the annual meeting of the American Public Health Association in November 1984 and is being prepared for publication. A main component of the series of studies on mesothelioma involves a case-control study of data from the New York State Registry, the University of Southern California and the Medical Follow-up Agency of the National Research Council. Reports are being prepared on the relationship to occupation, the results of a review of pathology specimens on file and findings concerning the personal and family histories of cases vs. neighborhood controls for risk factors other than exposure to asbestos.

Agent Orange

Dr. Miller serves as chairman and Dr. Julianne Byrne as Executive Secretary of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, which reports to the Chairman of the Cabinet Council Agent Orange Working Group. This Advisory Committee of non-government specialists oversees massive studies of the health effects of Agent Orange. During the year, the Committee was strengthened by the addition of experts in scientific design, psychology, psychiatry and neurology. A project site visit was made to the Air Force group responsible for the Ranch Hand study, and an evaluation written. Earlier in the year, a critique was prepared concerning the verification from hospital records of birth defects reported by the parents in the Ranch Hand vs. the control group. The Committee also advises on studies of Agent Orange by the Centers for Disease Control (CDC). A critique was prepared for its study of birth defects among children whose fathers were Vietnam veterans vs. controls. The Advisory Committee is concerned with both the medical/biologic rationale of the studies of Agent Orange and the analysis of the results.

Family Studies

Fanconi-like Syndrome: Because Fanconi's anemia is due to an autosomal recessive gene, it rarely occurs over two generations in a family. The parents of an affected child are asymptomatic carriers. In patients with the syndrome, acute monomyelogenous leukemia (AMML), a rare form of leukemia, occurs excessively. Dr. Carol Alter, then a medical student on elective in our Branch, ascertained a family in which the index case, a young woman with AMML, had elements of the syndrome: short stature, skin hyper-pigmentation, ureteral anomalies treated surgically during childhood, and late-occurring moderate hypoplasia of the marrow. The chromosomes in lymphocytes were not unstable in culture as in typical Fanconi's anemia. The patient's sister had the same appearance, marrow hypoplasia, ureteral anomaly and pigmentation. Their father and his brother had died young of a marrow dysplasia. The sisters had severe periodontitis, and the index case had one child who at two years of age is of short stature, but has a large head. Special laboratory studies are in progress to determine if the sisters have Fanconi's anemia, and to define by in vitro techniques the functional capacity of the surviving sister's white blood cells. If the laboratory studies support the diagnosis of Fanconi's anemia, a variant form will have been

described. If not, the case will be compared with others less well defined in the literature to determine if an entity exists that looks like, but is distinct from Fanconi's anemia. Dr. Alter's preceptor was Dr. Levine, assisted by other members of the Branch.

Breast Cancer in Black Families: Two black families have been ascertained with high frequencies of breast cancer. One was found by Dr. Patricia Siraganian, then a medical student on elective in our Branch. Four generations have been affected. The risk rises in the line of descent as each new case is diagnosed, and the risk is further raised when previous cases were young at diagnosis, had bilateral cancers and/or fibrocystic disease. The risk can be estimated for simple familial aggregates of breast cancer among whites, but the data for making such estimates for black families do not exist. Our observations will be prepared for publication to call attention to these limitations in current knowledge. Dr. Siraganian's preceptor was Dr. Levine, assisted by other members of the Branch.

Etiologically Informative Consultations

Congenital PCB Poisoning in Taipei: An analytical review by Dr. Miller concerning the findings in congenital polychlorinated biphenyls (PCB) poisoning in Kyushu, Japan, in 1968 and Taipei in 1979 revealed that no comprehensive follow-up studies were being made. The sparse findings thus far revealed that the newborn infants were small for date, had transiently dark skin, cysts of the Meibomian glands, calcifications in the brain, and teeth present at birth. The pathogenesis of the disorder was ill-defined. The natal teeth seemed to be a key finding. The review was presented at a workshop held by National Institute of Environmental Health Sciences (NIEHS), at which the most recent findings of congenital PCB poisoning in monkeys were reported, including thin dental alveolar ridges with cysts underneath that caused the unerupted teeth to deviate from their natural course. As a result of the workshop, staff members at NIEHS held two consultative meetings to plan a comprehensive follow-up study in Taipei, with special attention to the teeth, skin and neurological development. In this planning, Dr. Miller contributed substantially to the content of the study and the recruitment of an extremely effective Taiwanese nurse-coordinator for the field study, which was conducted in April 1985. The findings of a neuro-ectodermal disorder greatly enhanced understanding of the syndrome, as will be reported by NIEHS.

Woburn Leukemia Cluster: A special panel convened by local health authorities and CDC reviewed data on the continuing cluster of childhood leukemia in Woburn, Massachusetts, and the alleged concurrent cluster of eye-ear-brain malformations as reported in a survey by statisticians at the Harvard School of Public Health. Review of the specific malformations by Dr. Miller revealed that almost all of the excess affecting the eyes, ear and brain was due to strabismus, which was occurring with normal frequency in the exposed group as compared with only one-tenth the normal frequency in the comparison group.

Four Growth Excesses in One Child: A request was received for advice concerning treatment for an infant with bilaterally enlarged adrenal glands and hemihypertrophy. The attending physician did not think the child had Beckwith-Weidemann (visceral cytomegaly) syndrome because of the seeming absence of an umbilical hernia and large tongue. Further examination revealed both to be present but not pronounced. Within two weeks the child's adrenal glands clearly had nodules on ultrasound examination, and nodules were seen in the liver. Surgery showed the adrenal tumors to be benign, and the liver tumors to be

hemangioma. Thus, the child had four growth exceses: hemihypertrophy, benign tumors, hamartomas and visceral cytomegaly. The case reminded us that no progress has been made in explaining the disease process since we first described this constellation of associated growth disorders almost 20 years ago. Dr. Li is exploring ways to study tissues from patients with Beckwith-Weidemann syndrome and cancer, with special reference to oncogenes and growth factor genes.

Resource Development

With the help of the Assistant Secretary for Health, some progress has been made in obtaining from the SSA essential information for follow-up studies involving the study of hepatitis/liver cancer among veterans, as described above, and in identifying twins who served in Vietnam, in connection with studies of the effects of Agent Orange. A formal agreement has been signed which allows NCI, as an agency of the government, to provide its contractors, such as Westat, with mailing addresses obtained from SSA. An obstacle still remains, however, in redisclosure of SSA information to the Internal Revenue Service (IRS) in connection with follow-up studies. A formal arrangement apparently has to be worked out to assure that IRS will not use the information provided except to serve the research purpose. The General Counsel at NIH is helping to develop the necessary documents.

Dr. Beebe serves as Chairman of the Working Group on Epidemiology Data Resources. Two new functions have recently been added: 1) to facilitate research that uses Veterans Administration hospital indexes, 1963-81, which will be updated at intervals, and 2) to enhance use of master agreements with certain cancer registries. The purpose is to broaden the use of these resources by the various Branches in The Epidemiology and Biostatistics Program (EBP). Membership on the Working Group will be increased accordingly.

Dr. Beebe also serves as one of four NIH representatives on an advisory committee to the Director, NCHS, concerning applications to use the National Death Index and for general policies relating to this resource.

Honors and Awards

For his contribution to creating the radioepidemiology tables, Dr. Beebe received the NIH Director's award.

Dr. Miller was the Saul Lehman Visiting Professor of Pediatrics at Downstate Medical Center, Brooklyn, N.Y., October 8-13, 1984. He was a speaker at a symposium to dedicate a new cancer hospital in Seoul, Korea, on October 22-23, 1984, and at another to mark the hundredth anniversary of Danbury Hospital, Connecticut, on June 19, 1985.

CLINICAL STUDIES SECTION

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

Hereditary Cancers of Genitourinary Organs

Additional studies continue to be made of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Somatic cell hybrids have been used to isolate the derivative 3 and derivative 8 chromosomes. Contrary to the preliminary findings last year that the c-myc oncogene was present in triplicate, studies this year show that it has been translocated without duplication. To examine further the etiologic role of genes on chromosomes 3 and 8, specimens of 24 renal cell carcinomas have been collected for cytogenetic analysis. The data thus far indicate non-random rearrangements involving the short arm of chromosome 3.

The Familial Breast Cancer-Sarcoma Syndrome

Cytogenetic studies in progress indicate that a high proportion of cancers of connective tissue (soft-tissue sarcoma and mesothelioma) have deletions or rearrangements in the region of 3p21. This finding is the first clue to a possible mechanism in the genesis of the diverse cancers that occur in the syndrome. The site is near the suspected locus for small-cell carcinoma of the lung.

Wilms' Tumor in Five Cousins

Dr. Gail Bruns at Harvard is undertaking a gene linkage analysis of a family with Wilms' tumor in five cousins. The probe in the study is a polymorphic catalase gene which is adjacent to the Wilms' tumor locus on the short arm of chromosome 11. The family has long been known to the Clinical Studies Section and illustrates how an inventory of clinical cases with peculiarities of cancer occurrence can provide research opportunities as new laboratory techniques are developed.

Delineation of New Cancer Susceptibility Syndromes

While previously recognized syndromes are under study, work is in progress to identify new cancer susceptibility syndromes. These include a family with a dominantly inherited platelet deficiency disorder in at least 22 family members, six of whom reportedly had leukemia or lymphoma of dissimilar types, including one infant with acute monocytic leukemia and congenital neuroblastoma histologically confirmed at the Dana-Farber Cancer Center (Dowton, S. B. et al, Blood 65:557-563, 1985). Phenotypic manifestations included mild to moderate thrombocytopenia, bleeding time prolongation, and abnormal platelet aggregation, with normal platelet survival time.

Also under study is a family syndrome of brain tumors, colon cancer and lymphoma in children, a large kindred with bowel cancer starting at age 20 and several families in which Hodgkin's disease has aggregated.

Late Effects in Survivors of Childhood Cancer

Clinical observations have also been revealing late effects of cancer that appear as new treatment improves survival. In a follow-up study of Wilms' tumor survivors, an excess of low birth weight was found among the offspring of females but not of males who had been treated with abdominal radiation. Twenty-five percent of the newborn infants of female cancer survivors were affected. Possibly radiotherapy diminished the elasticity of the uterus, thus causing uterine

constraint in the growth of the fetus, or radiation-induced fibrosis caused vascular insufficiency of the uterus. An effect on the kidney, manifested as an increased frequency of hypertension, might have been expected due to radiogenic vasconstriction or nephritis, or from removal of one kidney as in renal donors, but a study by the Section showed no such excess among 119 adults who had been so treated for Wilms' tumor in childhood.

Retinoblastoma: Second Cancers after X-ray and other Therapy

Dr. Li, in collaboration with Dr. Boice of REB, NCI, is planning a follow-up study with Dr. Robert Ellsworth's group at New York Hospital and Dr. Thaddeus Dryja of Harvard Medical School of 1581 retinoblastoma patients treated up to 65 years ago at Columbia University or New York Hospital. About 1000 of these patients are being actively followed, and the remainder will be sought through resources available to CEB and REB. The occurrence of second primary cancers will be determined, and when found, confirmation of the diagnosis by review of the histologic specimens will be made. The influence of radiation dose, chemotherapy, hereditary aspects of etiology, age and sex will be evaluated with respect to the development of second primary cancers. If specimens can be obtained, Dr. Dryja, a molecular biologist, will study them.

Environmental Carcinogens

Studies in Boston have continued to examine environmental causes of human cancer. In collaboration with EEB, extension of an earlier study by the Branch of death-certificate diagnoses for female chemists, showed an excess of suicide by cyanide poisoning, and an excess of cancers of the breast and ovary.

A study of the geographic distribution of Hodgkin's disease in the United States revealed a continuing deficit of deaths in 11 southern states that is now in its third decade.

CLINICAL GENETICS SECTION

Laboratory Studies of Patients or Families at High Risk of Cancer

The Branch traditionally has identified persons or families at high risk of cancer; e.g., persons with multiple primary cancers, familial cancer or syndromes of congenital malformations. Scientists elsewhere have identified laboratory abnormalities in such patients, and the findings have led to new understanding of cancer biology. For example, the Wilms' tumor-aniridia syndrome was defined by CEB, the chromosomal deletion responsible was found by an investigator in Texas, and other investigators found evidence through molecular biology that deletion of the gene on the homologous chromosome removed control of normal renal development. As a result of this homozygous recessive deletion at the cellular level, neoplasia occurred. The same mechanism has been found for retinoblastoma, and new understanding of carcinogenesis was thus developed. To expedite these steps in the future, CEB made contracts with laboratories, mostly at universities, for studies of somatic cell genetics involving specimens obtained by the Branch from persons at high risk of cancer.

The oldest of the contracts, made in 1978 with Dr. Malcolm C. Paterson at Atomic Energy of Canada, Ltd. (AEC), yielded a variety of interesting findings, which have been described previously. In 1982, a similar interagency agreement was made

with Dr. Richard Setlow of Brookhaven National Laboratory (BNL) to study skin fibroblasts from females in Hiroshima who were exposed to the atomic bomb before 20 years of age and developed an excess of breast cancer when they reached the age when this cancer normally occurs. Also, studies will be made of specimens from Israelis who developed an excess of thyroid cancer after radiotherapy during childhood for tinea capitis. The estimated average dose to the thyroid was only nine rads, and a question has been raised about whether the high proportion of immigrants from North Africa in this group are unusually susceptible to radiogenic cancer because of the high frequency of ataxia-telangiectasia (AT) among families from Morocco. For each of the radiation-exposed groups, appropriate comparison groups have been selected from which specimens are also being obtained.

A Project Site Visit was held during the past year and both studies were favorably reviewed: "The site visit team ..... considers the Division of Cancer Etiology most fortunate to have the services of the AEC and BNL laboratories, both of which are first rate." It was decided, however, to continue only the interagency agreement with Dr. Setlow, and to collaborate with Dr. Paterson whose funds will come from other sources when he relocates during this summer.

Responsibility for the contract with Roswell Park Memorial Institute has been transferred from Dr. Parry to Dr. Li, who has been making the greatest use of it. The contract is for cytogenetic studies of tumor tissue. The specimens come from the Dana-Farber Cancer Center in Boston and from NIH. The NIH specimens are from soft-tissue sarcomas, of particular interest with respect to the Li-Fraumeni syndrome (soft-tissue sarcomas in more than one child, and cancers of the female breast, among other sites in close relatives).

Data for routine cytogenetics of peripheral lymphocytes from about 700 family members from 50 cancer families, studied under contract with Biotech Research Laboratories, is being reviewed by our research assistant, Ms. P. Madigan. She is determining the frequency of abnormalities chromosome-by-chromosome (1 through 22 plus X and Y).

Under the contract with Litton Bionetics, a study was made of spontaneous and mutagen-induced sister chromatid exchanges (SCEs) in fresh vs. frozen lymphocytes from 10 individuals. Cryopreservation over a six-month interval did not significantly alter the frequency of SCEs. When SCEs were induced by mutagens, the response was parallel for fresh vs. cryopreserved specimens. Smoking and gender had no effect. These findings indicate that frozen specimens (as from patients who are no longer available) can be used for the study of SCEs.

The frequency of SCEs is now being evaluated in the dysplastic nevus syndrome by Dr. M. Greene of EEB, and in the nevoid basal cell carcinoma syndrome by Dr. A. Bale of CEB.

The contract with Yale University for cytogenetic studies using prophase banding techniques was underutilized during the past year. The Principal Investigator has agreed to look during the coming year for evidence of oncogenes in sarcoma specimens. After determining the karyotype of the patient's lymphocytes, the laboratory will extract DNA from both lymphocytes and tumor. Probes with sequences from a variety of oncogenes and growth factors will be used to search

for gross rearrangements or amplification of oncogenes or growth factor genes in tumors as compared to normal (constitutional) DNA.

The above-mentioned contracts are used not only by CEB, but also by EEB and REB. Since the contracts were initiated, 308 specimens have been examined for genetic markers for linkage analysis by Dr. Robert Sparkes and his group at UCLA; 156 specimens from solid tumors have been studied cytogenetically by Dr. Avery A. Sandberg at Roswell Park Memorial Institute; 200 standard chromosome analyses have been made by Biotech Research Laboratories; 54 studies of prophase banding have been made by Dr. Uta Francke at Yale; 85 specimens have been submitted to Litton Bionetics for study of sister chromatid exchange rates; 103 specimens have been studied for in vitro sensitivity and DNA repair by Dr. Paterson and 91 by Dr. Setlow.

The NIH Interinstitute Medical Genetics Program

At the Medical Genetics Clinic held one morning each week, almost 300 patients are seen annually. About 30% are NCI patients. The patients are seen either because they are on protocol or on referral for the possibility of a genetic disorder that predisposes to cancer. The Clinic serves as a source of observations for new hypotheses about carcinogenesis and for specimens to be studied in the laboratory for clues to cancer biology in persons at exceptionally high risk. Main interests at present are in familial breast cancer, neurofibromatosis, and the nevoid basal cell carcinoma syndrome.

Nevoid Basal Cell Carcinoma Syndrome (NBCC): During the year, a special study of NBCC was begun. This disease, transmitted as an autosomal dominant disorder, is characterized by multiple basal cell carcinomas, skeletal anomalies, ectopic intracranial calcification, and pits of the palms of the hands and feet. Certain neoplasms other than skin cancer occur excessively in patients with the syndrome: medulloblastoma, benign and malignant ovarian tumors, and possibly cancer of the breast and colon. Discovery of the mechanism of action of the NBCC gene in carcinogenesis may lead to general understanding at the molecular level of the pathogenesis of basal cell carcinoma in the population at large and of other cancers.

A sensitivity to ionizing radiation with regard to the induction of basal cell carcinomas in the field of radiation has been described in at least four cases. Hence there appears to be a genetic-environmental interaction akin to that seen in ataxia-telangiectasia and retinoblastoma with respect to ionizing radiation, and xeroderma pigmentosum with respect to ultraviolet light. A battery of laboratory tests are being performed to map the NBCC gene locus, if possible, and to test cells in vitro for sensitivity to radiation and certain chemicals.

About five large multi-generational families with living members showing NBCC are under study. In addition to defining the characteristics of the syndrome and the cancers associated with it, and the studies of somatic cell genetics, a repository of cells from affected and unaffected members of the families is being created for use in collaborative studies of the molecular pathogenesis of the syndrome. The principal investigator is Dr. Allen E. Bale, with co-investigators from NCI's CEB, EEB, the Dermatology Branch, and the Cancer Prevention Studies Branch, as well as NIH staff members of the National Institute of Dental Research, the National Eye Institute, and the National Institute of Neurological and Communicative Disorders

and Stroke and the Department of Radiology of the Clinical Center. The study should be completed by May 1986.

Neurofibromatosis (NF): Specimens have been obtained from additional families with NF over several generations for gene linkage studies under the contract with Dr. Sparkes of UCLA. The results were presented by Dr. Parry at a symposium on NF at the New York Academy of Sciences on May 23-24, 1985. Also presented was a life-table for persons with the disease, and the occurrence of cancer among them and their relatives, as determined in a collaborative study between Dr. Mulvihill, CEB, and scientists at the Institute of Medical Genetics in Copenhagen. The data came from a follow-up study of 212 NF patients ascertained through hospitals in Denmark in 1944. A report has been submitted for publication.

Another collection of data from questionnaires sent to persons with NF through the NF Foundation is awaiting analysis with regard to paternal age of sporadic cases, as a measure of age-related mutations; and possibly development of a life-table for this non-hospital based series. The statistical analysis will be made, if possible, with a former co-investigator.

Studies of Late Effects among Survivors of Childhood Cancer

To evaluate the occurrence of second primary cancers and the reproductive performance of children and adolescents who survived cancer, a study was initiated in 1980 by the Biometry and Clinical Epidemiology Branches through contracts with five medical centers for telephone interviews of their 2305 childhood cancer survivors and 3299 sibling controls. Funds for the study came from the Biometry Branch, which was responsible for the statistical aspects, analysis of the results, and the report of second primary cancers. CEB was responsible for reports on the reproductive performance of the survivors. Analysis of the data has been handicapped by the transfer of the biometricians from DCE to DCPC in 1984, with a change in their duties. A further problem was created by career changes that led to the resignation of one young member from each Branch. The analysis of reproductive performance by CEB was greatly aided, however, by the recruitment in 1984 of Dr. Julianne Byrne, a reproductive epidemiologist.

During the past year, frequent meetings have been held between NCI investigators in both Branches under the leadership of Dr. Mulvihill to discuss each step in the analysis of the data. On April 10, 1985, the NCI group met in Houston with four of the five directors of the data collection at the cancer centers and two of three university-based consultants who had advised on the study at its outset. Plans were laid for a series of publications.

The addition of Dr. Byrne to our staff has greatly aided the study of fertility/infertility. Data from males and females in the five-center study are being treated separately in the analysis, making, in effect, two different studies. Three types of outcome are being evaluated: 1) the probability of marrying; 2) when married, the risk of becoming pregnant or of fathering a pregnancy; and 3) once pregnant, the risk of an adverse outcome. Adverse pregnancy outcomes to be studied include difficulty in becoming pregnant, secondary infertility, miscarriage, ectopic pregnancy, perinatal loss, small-for-date babies, preterm delivery, and birth defects. At each level a stratified analysis will elucidate the role of possible confounding variables.

Effect of Chemotherapy on Pregnancy Outcome

In January 1978, seventy-five physicians of Cancer and Acute Leukemia Group B, in responding to a questionnaire, reported on 66 women who had cancer at conception or diagnosed during pregnancy. The physicians then forwarded a questionnaire to the women, and the outcome of 133 pregnancies were thus ascertained. Forty-three pregnancies occurred before the women developed cancer, 32 during pregnancy, and 58 after therapy. The distribution by cancer type was: 76 Hodgkin's disease, 27 other hematopoietic neoplasms, and 30 patients with 8 other types of cancer. Among 10 liveborn infants exposed to chemotherapy during the first trimester one was born with cleft lip and palate and another with hydrocephalus. The other eight were normal. One stillborn had polydactyly. The percentage of various abnormal outcomes for this group was similar to that for the group of pregnancies before cancer was diagnosed, 28% and 23%, respectively. Among 50 pregnancies after therapy had stopped, 40% had abnormal outcomes, due largely to low birth weight and premature terminations of pregnancy in the first year post-therapy. A report of these findings has been submitted for publication.

Other Activities

Other original work published or in press during the year has been described in previous annual reports, and include an update of gene maps for neoplasia in man, neurofibromatosis--no chromosomal defect by prophase banding technique; plasma melatonin and the hormone-dependency of human breast cancer; the concurrence of Saethre-Chotzen syndrome and malignancy in a family with in vitro immune dysfunction; the availability of insurance to long-time survivors of childhood cancer; Sotos syndrome (cerebral gigantism) in a mother and her two daughters; and patterns of inheritance in hypertrophic cardiomyopathy. A case-report and comprehensive review of the literature submitted for publication concerns premature separation of the centromere as seen in a pair of sisters with SC phocomelia syndrome, one of whom had melanoma. An editorial was prepared for the New England Journal of Medicine on the inheritance of polyps of the colon. Overviews, published or in press during the year, concern the clinical genetics of cancer, clinical ecogenetics of cancer, occupational ecogenetics; mutation epidemiology and its prospects for detecting human germinal mutations; research vistas in the mutiple endocrine neoplasia syndromes; genetic susceptibility in the etiology of lung cancer; the genetic consequences of modern therapeutics; offspring of long-time survivors of childhood cancer; and a teratogen update on the fetal alcohol syndrome.

Symposium Being Planned

An international symposium is to be held in Bethesda in the Spring of 1986 on the reproductive aspects of human cancer, including gonadal dysfunction following cancer and its therapy, as well as possible teratogenicity and mutagenicity as seen in offspring of cancer patients. A planning meeting will be held on August 19, 1985. The co-organizers, Dr. J. J. Mulvihill of CEB and Dr. R. J. Sherins of NICHD, feel that the time is ripe to pool data, synthesize information, define challenges, and publish Proceedings to stimulate further work.

Awards and Honors

Dr. Parry was certified by the American Board of Medical Genetics as a Ph.D. Medical Geneticist.

U.S.-Italy Cancer Research Program

In 1984, Dr. Li assumed responsibility for an epidemiology component of the U.S.-Italy Cancer Research Program. The main areas to be explored were childhood cancer, childhood leukemia with a high frequency of hepatitis B infection in Italy and stomach cancer in an area of Italy with a very high frequency (a case-control study had already been initiated by Dr. Blot of the Biostatistics Branch). After the initial meeting between the two countries in 1984, Dr. Li arranged for a collaborative study to be made by the Fox Chase Cancer Center in Philadelphia, the Children's Hospital of Philadelphia and the Institute of Clinical Medicine at the University of Padua. The purpose is to investigate the etiology, prevalence and effects of hepatitis B virus and related viruses in children with acute leukemia. The studies of hepatitis and of stomach cancer are off to a good start. Groundwork needs to be developed for studies concerning other subjects. The next meeting, to be held in Bethesda in November 1985, will explore interest in common concerning biotechnology.

U.S. - Japan Activities

The Nakasone Program: Under the Nakasone Cancer Program, Shaw Watanabe, M.D., pathologist at the National Cancer Hospital Research Institute in Tokyo, spent three months in the Branch learning about clinical epidemiology. His objective was to increase his familiarity with clinical observations as a starting point for epidemiologic and other etiologic studies. Meanwhile he became interested in the SEER data and, in conjunction with Dr. John L. Young and Dr. Charles Brown, DCPC, is working on a manuscript concerning the cumulative incidence rate of (a) Hodgkin's disease by subtypes and (b) other hematologic malignancies. The differences in rates among them may have implications with regard to host susceptibility.

Workshop on Subtypes of Cancer: On October 16-17, 1984, a workshop was held in Honolulu to exchange ideas concerning the etiologic importance of studying cancer by subtypes. Even when cancers were classified grossly by location within an organ, important differences were noted between U.S. whites and Japanese; e.g., gastric cancer is the most common in the cardia among whites vs. other parts of the stomach among Japanese-Americans. Other ways of subclassifying cancer concerned tissue patterns, cytohistology, histochemistry, antigenic response--including cell-surface markers, ultrastructure, cell products and chemical receptors, biochemistry, cytogenetics and studies of DNA; clinically by familial vs. sporadic cancers, by response to therapy, and by host susceptibility; and epidemiologically by demographic or ethnic differences. A number of ideas for further study were thus generated.

Workshop on Cancer under Age 30: On March 11-13, 1985, a workshop was held in Tokyo on adult-type cancers under age 30. We thought that new understanding of the etiology or pathogenesis of cancer might come from studying its occurrence at an earlier age than usual. When the workshop was first proposed, it was judged by the Japanese side to be of special interest and was therefore augmented with support by the Nakasone Program.

In preparation for the workshop, participants from both countries prepared data from a variety of sources. SEER data were remarkably filled with clusters that invited further study. The epidemic of Kaposi's sarcoma in 1981-82 in San Francisco was detected, and DES-induced cancers of the lower female genital tract

were apparently discernable in the data for this site. These observations led to the belief that other clusters within the data-system may also be etiologically informative, and may in some instances relate to intrauterine exposure. Among the clusters observed were 29 cancers of the lip in white males vs. only 4 in females; 32 cancers of the gums and mouth among white females vs. 13 among males; and 31 cancers of the tongue under age 30 in U.S. whites, two-thirds affected the tip, as occurs in the genetic disorder, xeroderma pigmentosum. (And so it went, through each organ-system.) From the Japanese side we learned that there are, on the average, about 550 deaths annually from stomach cancer under age 30, eleven times more frequent than the number of new cases diagnosed among whites in the U.S. annually according to SEER data. The subtype of the cases in Japan is diffuse, rather than intestinal, a surprising observation because the diffuse type was thought to have a constant rate worldwide.

The Tumor Tissue Registries at the Radiation Effects Research Foundation in Hiroshima and Nagasaki provided data that indicated that this resource may become extremely valuable in the future when ascertainment is more complete and duplications have been excluded.

The U.S. participants learned that the Japanese have a substantial number of special disease registries, concerning, for example, polyps of the colon, bone cancer, soft-tissue sarcoma, xeroderma pigmentosum, melanoma, pineal tumors (which are about 12 times more frequent in Japan than elsewhere), children's cancer and thyroid cancer. The bone cancer registry revealed a marked deficiency in the frequency of Ewing's sarcoma in Japan as compared with the U.S., a finding previously unknown to many of the Japanese. The childhood cancer registry revealed that the relative frequencies differed markedly in the two countries with respect to neuroblastoma, Wilms' tumor and retinoblastoma. There was an excess of retinoblastoma and a deficiency of Wilms' tumor in Japan, possibly indicating differences in chromosomal susceptibility to deletion--greater among the Japanese for the long arm of chromosome 13, leading to retinoblastoma, and less for deletion in the short arm of chromosome 11, protecting against Wilms' tumor. In Japan, among the Wilms' tumor cases the frequency of aniridia was only about half as great as in the U.S., which suggests that the deletion is less frequent there than in the U.S. Geographic differences in the frequencies of chromosomal abnormalities associated with other cancer have been reported by Mitelman.

The existence of the thyroid tumor registry, unknown to the U.S. side, led to the realization that identifying information for atomic-bomb survivors could be matched against that for persons listed in the registry to find migrants from Hiroshima and Nakasaki who had developed this neoplasm, and thus improve the estimates of radiation risk. Overall, the list of suggested studies is long, and can begin in the U.S. with further studies of the SEER data.

Workshops for the coming year will concern a) the epidemiology of cancer in Southeast Asia and b) cancer of the urinary bladder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04377-14 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

COOPERATING UNITS *(if any)*

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

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

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

Major Findings:

Reports published or in press in the last 12 months by the two permanent participants of the project comprise ten reports of original research, nine reviews, and three abstracts for national meetings. Research reports involved co-authors from the Environmental Epidemiology, Medicine, Surgery, and Pathology Branches of the National Cancer Institute, the Clinical Center, the National Eye Institute, the National Institute of Dental Research, the Cleveland Clinic, the University of California at Los Angeles, Tulane University, and the Institute of Medical Genetics, Copenhagen, Denmark.

Interdisciplinary Studies on Neurofibromatosis. The Section has committed considerable resources to studies designed to clarify the genetics and natural history of neurofibromatosis (NF), an autosomal dominant disorder with protean manifestations including an increased risk of developing certain cancers.

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

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

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

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

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

Laboratory collaborations involving the study of cancer families have been useful in addressing other hypotheses of cancer etiology. Colleagues in the Medicine and Surgery Branches, NCI, found that the usually large day-night differences in plasma melatonin levels were absent in women just diagnosed with breast cancer, but only if it proved to have estrogen receptors. To clarify whether this abnormality was a concomitant of breast cancer or truly an antecedent to it, we recruited 23 women in 10 kindreds who were free of breast cancer but at very high risk of it owing to family history of the cancer. In comparison to 33 normal volunteer females and 37 with newly diagnosed breast cancer, there were not statistically significant differences in the diurnal cycle of melatonin levels, but a further quantitative inverse correlation was seen between estrogen- and progesterone-receptor levels and the peak-nadir difference in melatonin.

Immunologic collaboration was established in studying a family with a craniosynostosis syndrome with Epstein-Barr virus-related malignancies. Among 13 siblings, three sisters and their father had the Saethre-Chotzen syndrome, an autosomal dominant trait with craniosynostosis and asymmetric facies. One affected sister also had nasopharyngeal carcinoma; two nondysmorphic brothers had Hodgkin's disease, and another had seminoma with teratocarcinoma of the testis. Decreased in vitro lymphocytic proliferation to various mitogens was observed in both available siblings with tumor, one sibling with Saethre-Chotzen syndrome, and two clinically normal siblings and their father. Both parents and all siblings had normal karyotypes and no increase of antibodies to Epstein-Barr virus. The malformation syndrome and the various neoplasias segregated independently of each other and of 27 genetic markers, including HLA. The occurrence of malignancies in this family may be related to subclinical immune dysfunction.

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

Moroccan descent, who have an excess of thyroid cancer owing to childhood exposure to radiation for the treatment of tinea capitis.

Collaborations for research on sister chromatid exchanges were used to establish a basis for greater epidemiologic use of this phenomenon which has been a marker of population exposure to certain mutagens. Our Program has repositories of cryopreserved lymphocytes, but most published experience is with fresh whole blood cultures. Therefore, a large experiment was designed to correlate spontaneous and mutagen-induced sister chromatid exchanges in fresh and frozen specimens from the same persons. Preliminary analysis showed that whole blood cultures had consistently lower levels than purified lymphocytes, but that freezing lymphocytes for up to six mo ths had no further effect.

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

New features were reported in the Sotos' syndrome (cerebral gigantism) which, in prior case reports, has been associated with Wilms' tumor and hepatoblastoma. By intensive evaluation of family members (thus overcoming the bias of ascertainment of the proband), we could suggest that developmental delay may not be universally associated with ultimate intellectual impairment in the disorder and that the cephalometric radiographs may be of great diagnostic help. Finally, clinical observation of a brachydactyly E family with the Wolfram or DIDMOAD syndrome (Diabetes Inspidus, Diabetes Mellitus, Optic Atrophy, and Deafness) provided a suggestion that the genes for the two rare syndromes may be linked. This fruitful genetic insight from a "simple" genetic patient consultation demonstrated remarkably agile thought.

Synthesis. An editorial, published in New England Journal of Medicine, emphasized the ecogenetic origins of human cancer as illustrated by cancer families. A review of the cytogenetic abnormalities associated with human cancer revealed 11 chromosomes now associated with leukemia and seven with solid tumors. Two human cancer genes can be assigned with confidence: retinoblastoma to 13q and Wilms' tumor to 11p. Two book chapters on cancer genetics were published in the Proceedings of an International Workshop on Mutagenesis, Carcinogenesis, and Teratogenesis held in Shanghai and a UCLA Symposium on Cancer and Genes. Three additional book chapters provided comprehensive reviews of genetic factors in lung cancer and the fetal alcohol syndrome. Thoughts on future research in occupational ecogenetics, neurofibromatosis, the multiple endocrine neoplasia syndromes, and the genetics of nasopharyngeal carcinoma were published in conference Proceedings. Five papers by Dr. Julianne Byrne appeared, based on prior research, but partly prepared with Section resources.

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

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

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

Critical reviews of manuscripts were prepared for Johns Hopkins University Press, Blood, Cancer, Cancer Genetics and Cytogenetics, Genetic Epidemiology, Journal of the American Medical Association, Journal of the National Cancer Institute, and Teratology. Grant applications were critiqued for the Committee on Advanced Study and Research in China, The National Foundation-March of Dimes, and the Louisiana Cancer and Lung Trust Fund Board.

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

Significance to Biomedical Research and the Program of the Institute:

Epidemiologic surveys and detailed clinical and laboratory studies of families and individuals at high risk of cancer may help distinguish environmental and genetic influences in carcinogenesis. In addition, identification of high risk individuals has therapeutic implications, enabling surveillance and early diagnosis of neoplasms and genetic counseling for offspring.

Proposed Course:

The same approach will be continued. New laboratory methods and epidemiologic clues from other sources will be incorporated into the project as available. Especially close watch will be made for advances in viral oncology and monoclonal antibody techniques that deserve exploration with human material. Manuscripts are

in final preparation on pregnancy outcomes in cancer patients, a family with a new limb and cranial nerve defects syndrome with melanoma and premature centromere separation, a Wilms' tumor cell line derived from an adult with that embryonal tumor who also had endometrial and laryngeal cancers, and a patient with the newly delineated Kabuki make-up syndrome.

Publications

Bale, A. E., Drum, M. A., Parry, D. M., and Mulvihill, J. J.: Familial Sotos syndrome (cerebral gigantism): Craniofacial and psychological features. Am. J. Med. Genet. 20: 613-624, 1985.

Bale, A. E., Ludwig, I. H., Effron, L. A., and Zakov, Z. N.: Linkage between the genes for DIDMOAD syndrome and brachydactyly E. Am. J. Med. Genet. 20: 733-734, 1985.

Byrne, J. and Blanc, W. A.: Malformations and chromosome anomalies in spontaneously aborted fetuses with single umbilical artery. Am. J. Obstet. Gynecol. 151: 340-343, 1985.

Byrne, J., Blanc, W. A., Warburton, D. W., and Wigger, J.: Significance of cystic hygroma in fetuses. Hum. Pathol. 15: 61-67, 1984. Reprinted in Obstet. Gynecol. Surv. 25: 37-42, 1985.

Byrne, J. and Warburton, D.: Neural tube defects in miscarriages. Am. J. Hum. Genet. 36: 1205, 1984.

Byrne, J., Warburton, D., Kline, J., Blanc, W., and Stein, Z.: Morphology of early fetal deaths and their chromosomal characteristics. Teratology (In Press)

Danforth, D. N., Tamarkin, L., Mulvihill, J. J., Bagley, C. S., and Lippmann, M. E.: Plasma melatonin and the hormone-dependency of human breast cancer. J. Clin. Oncol. (In Press)

Gusella, J. F., Spence, M. A., Parry, D. M., Bader, J. L., and Doyle, S. Z.: Genetic linkage of neurofibromatosis using DNA markers. In Rubenstein, A. E., Bunge, R. P., and Housman, D. E. (Eds.): Neurofibromatosis. New York, New York Academy of Sciences. (In Press)

Hamilton, H. B., Ban, S., Nakamura, N., Hiraoka, T., Miller, R. C., Ezaki, H., Nishiki, M., Yamane M., Setlow R. B., Parry, D. M., Beebe, G. W., Mulvihill, J. J., and Land, C. E.: Host variation in susceptibility to radiation-induced breast cancer among atomic bomb survivors: A pilot in vitro study. RERF Research Protocol. Hiroshima, Radiation Effects Research Foundation, 1984, pp. 1-6.

Jahiel R., Byrne, J., Lubin, R., and Gorelick, J.: Handbook on Prevention of Mental Retardation and Developmental Disabilities. New York, Van Nostrand Reinhold Publishing Company. (In Press)

Kao, Y. S., Kao-Shan, C. S., Knutsen, T., Whang-Peng, J., and Mulvihill, J. J.: Neurofibromatosis: No chromosomal defect by prophase banding technique. Cancer Genet. Cytogenet. 13: 281-282, 1984.

McKeen, E. A., Mulvihill, J. J., Levine, P. H., Dean, J. H., and Howley, P. W.: The concurrence of Saethre-Chotzen syndrome and malignancy in a family with in vitro immune dysfunction. Cancer 54: 2946-2951, 1984.

Mulvihill, J. J.: Book Review: Inheritance of Susceptibility to Cancer in Man by Bodmer, W. F. Science 223: 162, 1984.

Mulvihill, J. J.: Clinical ecogenetics of cancer. In Bishop, J. M., Rowley, J. D., and Greaves, M. (Eds.): Genes and Cancer. UCLA Symposium on Molecular and Cellular Biology, New Series. New York, Alan R. Liss, Inc., 1984, Volume 17, pp. 19-36.

Mulvihill, J. J.: Clinical ecogentics: Cancer in families. N. Engl. J. Med. (In Press)

Mulvihill, J. J.: Clinical genetics of human cancer. In Chu, E. H. Y. and Generoso, W. M. (Eds.): Mutation, Cancer, and Malformation. New York, Plenum Press, 1984, pp. 13-34.

Mulvihill, J. J.: Genetic consequences of modern therapeutics. In King, R. A., Rotter, J. I., and Motulsky, A. G. (Eds.): The Genetic Basis of Common Disease. New York, McGraw-Hill. (In Press)

Mulvihill, J. J.: Lung cancer. In King, R. A., Rotter, J. I., and Motulsky, A. G. (Eds.): The Genetic Basis of Common Disease. New York, McGraw-Hill. (In Press)

Mulvihill, J. J.: Neurofibromatosis: A genetic epidemiologist's point of view. In Rubenstein, A. E., Bunge, R. P., and Housman, D. E. (Eds.): Neurofibromatosis. New York, New York Academy of Sciences. (In Press)

Mulvihill, J. J.: Research vistas in the multiple endocrine neoplasia syndromes. Henry Ford Hospital Med. J. 32: 277-282, 1984.

Mulvihill, J. J.: Update on "Teratogen update: Fetal alcohol syndrome." In Sever, J. L. and Brent, R, L. (Eds.): Teratogen Update. New York, Alan R. Liss, Inc. (In Press)

Mulvihill, J. J. and Bale, A. E.: Ecogenetics of lung cancer: Genetic susceptibility in the etiology of lung cancer. In Mizell, M. and Correa, P. (Eds.): Lung Cancer: Cause and Prevention. New York, Verlag Chemie International, 1984, pp. 141-152.

Mulvihill, J. J. and Madigan, P.: Neoplasia in man. In O'Brien, S. J. (Ed.): Gene Maps, Third Edition. New York, Cold Spring Laboratory, 1984, pp. 446-449.

Mulvihill, J. J., McKeen, E. A., Rosner, F., and Zarrabi, M. H.: Pregnancy outcome in cancer patients. JNCI. (In Press)

Sørensen, S. A., Mulvihill, J. J., and Nielsen, A.: 35-year follow-up of neurofibromatosis. In Rubenstein, A. E., Bunge, R. P., and Housman D. E. (Eds.): Neurofibromatosis. New York, New York Academy of Sciences. (In Press)

Spence, M. A., Parry, D. M., Bader, J. L., Marazita, M. L., Bocian, M., Funderburk, S. J., Mulvihill, J. J., and Sparkes, R. S.: Genetic linkage of neurofibromatosis. In Rubenstein, A. E., Bunge, R. P., and Housman, D. E. (Eds.): Neurofibromatosis. New York, New York Academy of Sciences. (In Press)

Ursell, P.C., Byrne, J., Strobino, B., Gersony, W. M., and Blanc, W. A.: Congenital heart disease among spontaneously aborted fetuses. Circulation 70: SII-426, 1984.

Warburton, D. and Byrne, J.: Estimates of the prevalence of chromosome anomalies expected in chorionic villus sampling procedures. In Brambati, B., Simoni, G., and Fabro, S. E. (Eds.): Fetal Genetic Diagnosis during the First Trimester of Pregnancy. New York, Marcel Dekker, Inc.. (In Press.)

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

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

Current Annual Level: $74,896

Person Years: 1.425

Objectives:

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

Major Contributions:

This year, 85 specimens have been submitted under this contract: whole blood = 66, bone marrow = 2, frozen lymphocytes = 2, spinal fluid = 1, lymphoblastoid line = 1, tumor cell line = 1, lymphocytes to transform with Epstein Barr virus = 12. The majority of peripheral blood specimens are from families with the nevoid basal cell carcinoma syndrome, both affected and unaffected indiviudals. We are currently engaged in a large clinical study of this disease. Ten of the 12 specimens to be transformed by Epstein Barr virus were also from these families. The twelfth specimen to be transformed was from a now deceased patient with leukemia associated with a familial syndrome of what may be a variant form of Fanconi anemia. To date, no strikingly unusual cytogenetic findings have been detected in any of these patients.

Proposed Course:

We will continue to submit specimens from patients with cancer, or at high risk of cancer, for routine cytogenetic analysis. Abnormalities found in individuals with tumors will be looked for in other family members and in unrelated individuals with the same tumor type. This contract will end on June 29, 1987.

YALE UNIVERSITY (NO1-CP-21037)

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

Current Annual Level: $85,677

Person Years: 1.14

Objectives:

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

Major Contributions:

During this year, the laboratory has been sent peripheral blood on 32 patients, and tumor specimens from 2 patients.

Analyses have been completed on 26 of the peripheral blood specimens. No cytogenetic abnormalities were found in 20 patients with the following clinical diagnoses:

Wilms' tumor and hemihypertrophy	1
Members of a renal cell carcinoma family	6
Members of a hairy cell leukemia family	3
Members of a Hodgkin's disease family	2
Melanoma and dysplastic nevus syndrome	2
Bilateral partial aniridia	1
Acute lymphocytic leukemia secondary to sarcoma	1
Nevoid basal cell carcinoma syndrome and neuroblastoma	1
Mother and sister of patients with testicular cancer	2
Father of patient with mental retardation, multiple congenital anomalies	1

Among other individuals, a patient with von Hipple-Lindau disease and renal cell carcinoma was found to have a constitutional inversion of chromosome 15 [inv(15)(p12q22.3)]. Since she was the only patient yet studied from her family, it is unclear whether the inversion and/or syndrome and cancer are related. Dr. Li is following up this family to obtain blood specimens from additional family members.

Cultured lymphocytes from the father of the two boys with testicular cancer had a few chromatid breaks and gaps. Both sons had numerous cells with cytogenetic abnormalites, probably secondary to treatment for their cancers.

The tumor specimens had been previously studied at Biotech (where the cell lines had been established) but analyses in the Yale laboratory revealed additional cytogenetic abnormalities.

The melanoma cell line from a patient with Roberts-SC phocomelia syndrome had a modal chromosome number of 82/83, with at least three copies of every chromosome

except the X, and four marker chromosomes involving chromosomes 3, 7, 9 and 13. Premature centromere separation was seen less often in these cells than in the patients' peripheral lymphocyte chromosomes.

The Wilms' tumor cell line had translocations involving chromosomes 4 and 14, 5 and 7, and 3 and 22. The ascitic fluid from the same patient had t(4;14) and t(5;7) and a different translocation involving chromosomes 3 and 4. Dr. Francke thinks that both of these cell lines will be useful in gene localization studies.

Proposed Course:

In addition to continuing to submit peripheral blood specimens from cancer patients and family members and selected tumor cell lines for further cytogenetic clarification, we have embarked on a small pilot project with Dr. Francke whose purpose is to look for evidence of oncogenes in sarcoma specimens. For selected sarcoma patients, lymphocyte karyotypes will be determined and Southern blots prepared from both lymphocyte and tumor specimens will be probed with sequences from a variety of oncogenes or growth factors. The goal of this pilot study is to determine if we can detect gross rearrangements or amplification of oncogenes or growth factor genes in tumors as compared to normal (constitutional) DNA. The contract expires on September 29, 1987.

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

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

Current Annual Level: $41,526

Person Years: 1.38

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

Major Contributions:

The laboratory has been sent 83 tumor specimens (including cell lines) in the past year. Tumor types for which more than one specimen has been submitted include: soft tissue sarcomas (18 cases), renal cell carcinoma (14), mesothelioma (7 plus 3 cell lines), melanoma (4), colon cancer (4), testes cancer (3), schwannoma (2), CLL or pre-CLL (4), hairy cell leukemia (4), basal cell carcinoma (3) and unspecified leukemia (2). Single specimens have been submitted of lipoma, Ewings sarcoma, gastric tumor, bladder cancer, brain tumor, lung cancer, Hodgkin's disease, histiocytoma, pheochromocytoma, lymphosarcoma and lymphoma. Four other tumors were of unspecified types.

The most successful analyses have been carried out on the mesotheliomas and renal cell carcinomas. From these studies, it appears that breaks or rearrangements

involving band q13 of chromosome 11 may be of etiologic importance in the development of mesotheliomas, while breaks or rearrangements involving chromosome 3p are of importance in the development of renal cell carcinoma.

Proposed Course:

Tumor specimens will continue to be submitted to this laboratory as they are available. Efforts will be made to obtain several different tumor specimens from patients with any tumors that appear to have unique and possibly characteristic chromosome changes. The current contract will continue until July 20, 1987.

LITTON BIONETICS, INC. (NO1-CP-21035)

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

Current Annual Level: $97,430

Person Years: 1.61

Objectives:

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

Major Contributions:

A large experiment has been completed whose purpose was to provide the needed baseline information for future SCE studies. The experiment compared the effects of sex, smoking history and in vitro mutagen exposure on SCE in fresh blood cultures, in fresh purified lymphocytes, and in lymphocytes frozen for one and six months.

The experiment was run on samples from 10 normal volunteers (five males, five females), half of whom were smokers. The effects of three doses each of mitomycin C, methyl nitrosourea, and 4-nitroquinoline-1-oxide were studied for each sample (whole blood, fresh lymphocytes, and lymphocytes frozen for one and six months) and compared with water and dimethylsulfoxide controls. In addition, each dose of each mutagen was studied in replicate cultures, each handled in one of two different ways, each designed to distinguish repair of bromodeoxyuridine damage.

The results to date indicate that:

1. cryopreservation over a 6 month interval did not significantly affect spontaneous SCE,

2. mutagen-induced SCE responses were parallel for purified and cryopreserved samples,

3. SCE for either whole blood or purified lymphocytes did not significantly fluctuate over time, and

4. no effect of gender or smoking on SCE was detected in the sample group examined.

With the successful completion of these studies, frozen lymphocyte specimens from approximately 80 individuals from cancer families have been submitted for evaluation of SCE. The major patient groups represented are the dysplastic nevus syndrome and melanoma, the basal cell carcinoma syndrome, and a variety of sarcoma families. Results on these specimens are pending.

Proposed Course:

We will continue to submit specimens from patients under study for SCE evaluation. If negative or inconsistent results are obtained after the appropriate analyses have been done, we will consider terminating this contract. The current contract expires on September 8, 1987.

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

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

Current Annual Level: $37,725

Person Years: 0.428

Objectives:

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

Major Contributions:

This year, the laboratory has received and processed blood and serum specimens from 183 persons. The following categories of specimens have been submitted:

Disorder	Number of Families	Number of Specimens
Nevoid basal cell carcinoma syndrome	5	59
Neurofibromatosis	4	71
Spinocerebellar ataxia	1	16
Fibroblast lines		6
Other families	4	31

Through a predecessor of the present contract, we collaborated with this laboratory to undertake a genetic linkage study of 11 multigeneration families with neurofibromatosis (NF). Of the 28 polymorphic markers studied at that time, the highest lod score (Z = 0.89) was for GC, located just distal to the centromere on 4q. Six informative families contributed to this result: five of them had a combined lod score of +2.2 for close linkage with GC; however, the sixth family had a lod score of -1.63. Although heterogeneity among these families was not demonstrated statistically, these disparate lod scores suggest that it is a possibility. We have therefore continued to ascertain NF families to investigate these linkage relationships further. Additional data from 8 families, for a total of 19 families, failed to strongly confirm possible linkage to GC, but also falied to suggest linkage with any other studied locus. Linkage studies of DNA polymorphisms in many of these families are now ongoing.

Linkage analysis of polymorphic markers in a large family with a possibly new form of olivopontine spinocerebellar ataxia suggests that this autosomal dominant form of herediatry ataxia is not the same as the one linked to HLA, since the lod scores to HLA and GLO are strongly negative. These findings suggest genetic heterogeneity.

Preliminary linkage analysis of polymorphic markers in the 5 families with the nevoid basal cell carcinoma syndrome suggest possible linkage of the disease to amylase on chromsome 1p. Dr. Bale will continue to accrue additional families with this syndrome to continue linkage studies with both the proteins variants and DNA restriction fragment length polymorphisms.

Proposed Course:

The laboratory will continue to receive specimens from appropriate families for polymorphic marker studies and segregation and linkage analysis.

ATOMIC ENERGY OF CANADA, LTD (NO1-CP-21029)

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

Current Annual Level: $320,546

Person Years: 6.97

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 gamma radiation or chemically induced DNA damage, and when repair defects are found, to identify the repair pathways involved and the cellular cause of the repair defects.

Major Contributions:

This laboratory is completing its last contract year with us. Consequently only 12 new fibroblast strains have been submitted this year to bring the total strains examined by this group to 103. Of these, 13 were from normal controls and 90 were from members of cancer families or individuals with unusual histories of cancer.

Much of the year has been spent completing studies to determine the cellular mechanisms responsible for the resistance to gamma radiation, mitomycin C, and methyl nitrosourea seen in fibroblasts from members of two sarcoma families. In one family, the uptake and activation of both mitomycin C (MMC) and 4-nitro-quinoline-1-oxide (4NQO) are the same as in controls, indicating equivalent DNA damage; thus, the strains are truly hyperresistant. In the second family, the best studied strain is defective in the intracellular ability to activate both MMC and 4NQO, so its hyperresistance to the effects of these agents differs in origin from that in the first family. These and other findings are being prepared for publication.

Proposed Course:

The current contract terminated on June 29, 1985.

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

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

Current Annual Level: $250,000

Person Years: 3.8

Objectives:

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

Major Contributions:

This laboratory is working on completing the analyses of the 92 fibroblast lines that have been sent to them since the initiation of this contract. In addition to strains from cancer families, these include approximatley 35 strains from Japan. The latter are from four groups of individuals: those with cancer and either high or low exposure to the atomic bomb, and those without cancer and either high or low atomic bomb exposure. To date, no striking abnormality has been identified in any member of a cancer family. At least one Japanese strain has had an abnormal response to both X-rays and chemical mutagens, but until tests on all Japanese strains have been repeated twice, the code will not be broken to determine into which exposure group this specimen falls.

Proposed Course:

The studies described above will be completed and cell lines that exhibit consistent abnormalities will be studied in detail to determine the cellular mechanisms responsible for the abnormal findings. Additional cell lines from cancer patients and high risk individuals will be submitted for study as appropriate. This interagency agreement has been extended for one additional year, until September 27, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04400-20 CEB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

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

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Clinical Epidemiology Branch

SECTION
Clinical Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

F. P. Li	Chief, CSS	CEB NCI
R. W. Miller	Branch Chief	CEB NCI
J. J. Mulvihill	Chief, CGS	CEB NCI
D. M. Parry	Geneticist	CEB NCI

Objectives:

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

Methods Employed:

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

Major Findings:

1. Work is in progress to identify biologic mechanisms of cancer susceptibility in disease syndromes identified by the Branch. In a family with an inherited 3:8 translocation associated with renal carcinoma in ten relatives, clinical follow-up has revealed development of new primary renal cancers in two previously affected individuals. Two others with renal cancers have also developed thyroid cancers. In laboratory studies, somatic cell hybrids have been used to isolate the derivative 8 and derivative 3 chromosomes. Probes with the c-myc oncogene indicate that this fragment has been translocated, but not duplicated as suggested by earlier in situ hyoridization studies. To further examine the etiologic role

of genes on chromosome 3 and chromosome 8, specimens of 24 renal cell carcinomas have been collected for cytogenetic analysis. Available data indicate non-random rearrangements of the 3p region in renal cancers. This region is also known to be involved in oat cell carcinoma of the lung, mesothelioma and rhabdomyosarcoma.

2. In studies of the familial breast cancer-sarcoma syndrome, chromosome analysis of connective tissue tumors (soft-tissue sarcomas and mesotheliomas), revealed the 3p21 region to be deleted or rearranged in a high proportion of cases. These changes were unexpectedly detected in two benign connective tissue tumors as well.

3. A linkage analysis is in progress on a family with Wilms' tumor in five cousins. The analysis employs a polymorphic catalase gene identified by Dr. Gail Bruns at Harvard Medical School. The catalase gene is adjacent to the Wilms' tumor locus on chromosome 11p and is being examined for linkage to Wilms' tumor occurrence in these cousins.

4. While previously recognized syndromes are under study, work is also in progress to identify new cancer susceptibility syndromes. These include a family with a dominantly inherited platelet deficiency disorder in 22 individuals and susceptibility to leukemia and lymphoma which developed in five of these patients. A new syndrome of familial brain tumor, colon cancer and lymphoma in childhood is also under study. In a large kindred with bowel cancer starting at age 20, follow-up of an affected individual since 1976 revealed recent development of colon cancer at age 22 in one additional patient.

5. Several families with Hodgkin's disease have been ascertained and will be examined for DQ1, an HLA D haplotype which to date has been found in all Hodgkin's disease patients in seven multiple-case families.

6. In our follow-up studies, attention has recently been focused on Wilms' tumor survivors. Among women who had received abdominal radiation for this tumor, 25% subsequently bore offspring of low birth weight. The effect was not seen in offspring of irradiated males. The low birth weight may be due to damage to the reproductive apparatus in young girls treated for Wilms' tumor with radiation. In a second study, 119 adults who had Wilms' tumor in early childhood were examined for frequency of hypertension, a reported complication of unilateral nephrectomy and radiation to the residual kidney. Although hypertension was found in individual patients, the frequency of this complication was not clearly excessive.

7. Developmental activities have been instituted to study risk of second cancers in 1500 retinoblastoma patients in New York and 300 retinoblastoma patients in Boston. Recent data suggest a 90% risk of a second cancer in hereditary retinoblastoma patients by 40 years of age. We will endeavor to collect tumor specimens for genetic studies.

8. Among our investigations of environmental causes of cancer, one, a study of female chemists who may have had exposure to diverse chemical carcinogens, revealed an excess of breast cancer and cancer of the ovary. There was also an excess of suicide by cyanide poisoning, a previously observed finding in a smaller study. In a study of the geographic distribution of Hodgkin's disease in the United States, a deficit of deaths in 11 southern states was found to have been present for more than three decades.

Significance to Biomedical Research and the Program of the Institute:

The Clinical Studies Section identifies persons susceptible to cancer for laboratory studies of mechanisms of carcinogenesis. Recently, attention has focused on the role of chromosome rearrangements and oncogenes in several human solid tumors and the use of molecular probes in linkage analysis of cancer families. In addition, specialized laboratory techniques are investigated as markers to identify persons for surveillance for cancer at early stages. Follow-up studies of survivors detect late effects of disease and therapy that may lead to modifications of therapy to reduce morbidity.

Proposed Course:

The Clinical Studies Section intends to continue studies of childhood cancers. These projects will examine the etiologic role of genetic factors and prenatal exposures, and the late effects of these diseases. In addition, the methods that have proved useful in childhood cancer studies will be applied to study appropriate cancers in adults. These studies will examine family aggregates of cancer and epidemiologic features of rare and seldom studied forms of adult malignancies. High risk persons will continue to be surveyed to detect cancer at treatable stages and to receive counseling and supportive care. Studies of tumor tissues have found non-random changes of chromosome 3p in renal carcinomas and mesothelioma. Methods of molecular genetics will be employed to pursue these findings.

Publications

Bader, J. L., Li, F. P., Olmstead, P. M., Strickman, N. A., and Green, D. M.: Childhood malignant melanoma: Incidence and etiology. Am. J. Pediatr. Hematol. Oncol. (In Press)

Dowton, S. B., Beardsley, D., Jamison, D., Blattner, S., and Li, F. P.: Studies of a familial platelet disorder. Blood 65: 557-564, 1985.

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

Gimbrere, K., McKay, F. W., and Li, F. P.: Geographic pattern of Hodgkin's disease in the United States. JAMA. (In Press)

Li, F. P.: Adverse effects of treatments--second cancers. In Devita, V. T., Hellman, S., and Rosenberg, S. A. (Eds.): Principles and Practice of Oncology. 2nd Edition. New York, J. B. Lippincott Company, 1985, pp. 2040-2049.

Li, F. P.: The chronic leukemias: Etiology and epidemiology. In Wiernik, P. H., Canellos, G. P., Kyle, R. A., and Schiffer, C. A., (Eds.): Neoplastic Diseases of the Blood. (In Press)

Li, F. P.: Genetic and familial cancer: Opportunities for prevention and early detection. Cancer Detect. Prevent. (In Press)

Li, F. P.: Patients at high risk of cancer of the large bowel. In Steele, G. and Osteen, R. T. (Eds.): Colorectal Cancer: Current Concepts in Diagnosis and Treatment. (In Press)

Li, F. P.: U.S.-Chinese cooperation in cancer research. China Exchange News 13: 1-3, 1985.

Li, F. P. and Bader, J.: Epidemiology of cancer in childhood. In Oski, F. and Nathan, D. G., (Eds.): Hematology of Infancy and Childhood. 3rd Edition. Philadelphia, W. B. Saunders Company. (In Press)

Li, F. P., Danahy, J., and Gelman, R.: Utility of differential leukocyte counts in cancer management. JAMA 252: 1312-1314, 1984.

Walrath, J., Li, F. P., Hoar, S. K., Mead, M. W., and Fraumeni, J. F., Jr.: Causes of death among female chemists. Am. J. Public Health. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05139-05 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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, CGS	CEB	NCI
	A. E. Bale	Medical Staff Fellow	CEB	NCI
	P. H. Levine	Senior Investigator	CEB	NCI
	M. A. Abraham	Research Assistant	CEB	NCI

COOPERATING UNITS *(if any)*

CC (S. Schlesinger); NEI (M. Kaiser-Kupfer); NIADDK (D. Camerini-Otero, B. White); NICHD (M. Zasloff); NIDR (K. Brown, A. Drum); NINCDS (R. Eldridge)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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 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 471 individuals representing some 60 different diagnostic categories. Of these, 191 patients (40%) were seen by members of CEB. For our Branch, the Clinic provides a multidisciplinary setting in which to study unusual patients who either have cancer or an increased risk of developing malignancy. Patients are ascertained through special referrals from outside physicians and inhouse requests for etiologic consultations. With informed consent, the approach to the patient includes detailed physical examination and, where applicable, epidemiologic studies of the environmental and genetic background and laboratory studies to clarify biologic mechanisms of carcinogenesis. Categories include patients with genetic diseases predisposing to malignancy, patients with birth defects and cancer, families with childhood sarcomas and breast cancer in blood relatives, and any other families with an excessive occurrence of cancer of any type.

PROJECT DESCRIPTION

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

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

Objectives:

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

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

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

Methods Employed:

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

Clinic Patients Seen by Members of the Clinical Epidemiology Branch

Patients with or predisposed to cancer: 163

Basal cell nevus syndrome	68		
Neurofibromatosis	62	Other familial leukemia	3
Women at high risk of breast cancer	6	Familial melanoma	1
		Familial Hodgkin's disease	4
Leukemia with possible ataxia-telangiectasia	1	Familial brain tumors and breast cancer	2
Leukemia with possible variant Fanconi's anemia	2	Tuberous sclerosis	7
Familial acute lymphocytic leukemia	7		

Birth defect syndromes or cytogenetic abnormalities: 14
Other diagnoses: 14

Major Findings:

1. We are continuing to ascertain and study members of three generation families with neurofibromatosis (NF) in an attempt to localize the NF gene. Preliminary linkage studies with 28 polymorphic protein markers in 11 families suggested a tentative gene localization to chromosome 4q. Eight new families were studied during this year. The combined data on all 19 families did not provide strong evidence for the occurrence of a gene for NF on chromosome 4, or on any other chromosome region for which we had genetic markers. Since our families are fairly small, we cannot statistically exclude the possibility of genetic heterogeneity. In addition to continuing to assay polymorphic enzyme markers, blood from newly ascertained families is being used to isolate DNA for study of the segregation of restriction fragment length polymorphisms and NF in these families. To date, in four studied families, there was no evidence of co-segregation of the NF phenotype with DNA probes for chromosome 4. However, these results are not conclusive, since the chosen families did not show any suggestion of chromosome 4 linkage with the standard polymorphisms. The studies with the chromosome 4 probes will now be done with some of the families in which evidence for linkage of NF with chromosome 4 was suggested in our original data. See Project Z01CE04377-14 CEB (Congenital, Genetic, and Familial Factors in Human Cancer) for publication.

2. Two members of the Branch are part of the interinstitute group which is overseeing a study, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), of cognitive and neurologic function in children with NF between the ages of 6 and 18 years. Unaffected sibs of similar age will serve as controls. Since the physical manifestations of NF can be subtle, we are utilizing our considerable clinical experience with this disease to screen NF families to identify appropriate study subjects.

3. Dr. Allen Bale is the director of a large clinical investigation of the nevoid basal cell carcinoma syndrome (NBCC). This autosomal dominant disorder is characterized by multiple basal cell carcinomas, keratocysts of the jaw, pits of the palms and soles, and skeletal malformations. In addition, both medulloblastomas and ovarian tumors occur to excess in the syndrome and several other neoplasms have been reported. In order to learn more about the effects of the nevoid basal cell carcinoma gene and its mechanism of action, we are studying several large NBCC kindreds. The immediate goals of the project include defining the spectrum of associated neoplasms and congenital malformations and searching for laboratory markers. We intend to follow up on previous studies suggesting radiation sensitivity, chromosome fragility and an increase in sister chromatid exchanges. Gene mapping by linkage analysis of polymorphic protein markers is underway, and a repository of frozen lymphocytes and fibroblasts will provide DNA for linkage analysis with restriction fragment length polymorphisms and for future molecular studies.

4. Sotos syndrome (cerebral gigantism) has occasionally been associated with malignancy. We saw a family with this disorder in our clinic, and Dr. Bale has prepared a report on them for publication. This family is remarkable as a bona fide instance of an affected mother with two affected offspring, strengthening the likelihood of autosomal dominant inheritance. Dr. Bale has contributed to the delineation of the syndrome by documenting growth patterns and the discrepancy in intelligence testing, which indicates greater depression of language than of motor skills. See Project Z01CE04377-14 CEB for publication.

5. In conjunction with an investigator from NINCDS, Dr. Bale has studied a multigeneration kindred with a possible new form of olivopontine spinocerebellar ataxia. Preliminary linkage analysis of polymorphic enzyme markers in this family suggests that this autosomal dominant form of ataxia is different from the one linked to HLA, since the lod scores to HLA and BF are strongly negative. Rather, this form may be linked to the ABO locus. These findings suggest genetic heterogeneity.

Significance to Biomedical Research and the Program of the Institute:

The Clinic provides a unique multidisciplinary setting in which unusual occurrences of cancer can be identified and studied by geneticists, epidemiologists and laboratory investigators. Through their experiences in the Clinic, graduate physicians become aware of and are instructed in methods of studying unusual occurrences of cancer that involve the integrated collaboration of clinic and laboratory personnel. The regular post-clinic conferences and seminars provide major vehicles for dissemination of new findings in cancer etiology to scientists representing a broad array of clinical and laboratory expertise and offer opportunities to establish future insightful collaborations.

Proposed Course:

The Genetics Clinic will continue to provide a unique setting for the study of genetic and environmental factors predisposing to increased cancer susceptibility. In our effort to learn about the causes of cancer, we will continue to ascertain and study patients with genetic diseases predisposing to cancer, familial aggregates of cancer, and patients with birth defects or unusual environmental exposures associated with tumor development. The Genetics Clinic will continue to train physicians to study genetic and environmental factors predisposing to increased cancer susceptibility.

Publications

See Project Z01CP04377-14 CEB.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05146-06 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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, CGS	CEB	NCI
Others:	J. M. Byrne	Epidemiologist	CEB	NCI
	M. H. Myers	Statistician	BB, DCPC	NCI
	R. R. Connelly	Statistician	BB, DCPC	NCI

COOPERATING UNITS *(if any)*

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

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.6	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 cancer and of men and women who reproduced during cancer therapy, are studied for information on the possible mutagenicity and teratogenicity of cancer treatment and to discover hereditary patterns of cancer. Current phases include intensive analysis of data from interviews and medical records of 2,285 survivors of childhood and adolescent cancer and their siblings (as 3,266 of controls) to gather information on subsequent morbidity and mortality (especially additional neoplasms), quality of life, fertility and health of offspring. Four percent of cases had subsequent cancer compared to 2% of the controls. In 7,117 offspring, 18 cancers occurred, sometimes in known patterns of single gene traits and cancer family syndromes. Half as many survivors as controls never had a pregnancy. In the subset of study subjects in Kansas, the 101 survivors had more difficulty than same-sex siblings in getting life and health insurance. In the Connecticut subset, 450 survivors encountered rejection from military service, college, and employment more often than siblings, but had the same frequency of major depressive episodes. A second phase is the completion of analysis of a voluntary registry of pregnancies in women with cancer that shows little, if any, excess of birth defects, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. A workshop was convened in Oslo, sponsored by the Norwegian Cancer Society and the U.S. Department of Energy, to explore interest in European collaboration in collecting additional data. Plans were laid for an International Conference on Reproduction in Human Cancer.

PROJECT DESCRIPTION

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

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

Objectives:

To document fertility and reproductive outcome in patients who become pregnant before, d ring, 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 counseling of long-time survivors of cancer. The hypothesis being examined is that cancer patients have excessive morbidity due to additional malignancies or other illnesses and impaired reproductive performance, including an increased frequency of live offspring with birth defects or cancer.

Methods Employed and Major Findings:

Three separate phases are in different stages of completion.

1) Intensive interviewing and record abstracting in five collaborating centers are complete on 2,285 individuals who had cancer under age 19 years, survived at least five years, and achieved at least age 18 years. The controls, 3,266 siblings of cases, were also studied for subsequent morbidity, mortality, quality of life, fertility and health of offspring. Intense analysis is underway. Preliminary tabulations showed that, in comparison to controls, the survivors less often perceived their health as good to excellent and more often were unable to work or marry, but had smoked less and had similar frequency of high school graduation and birth defects in offspring. New cancer occurred in 4% of cases, 2% of controls, and in 18 of 7,117 offspring. Some families had retinoblastoma, Wilms' tumor, medullary thyroid carcinoma, or other known or suspected patterns of familial cancer. The survivors, more often than controls, reported never having initiated a pregnancy, at a statistically significant relative risk of 1.5 in both males and females. Among those ever pregnant, the average number of pregnancies was 2.4 in the 1,268 survivors and 2.6 in the 2,272 appropriate controls ($p < 0.02$). There were no differences in the rates of miscarriages, stillbirths or ectopic pregnancies, but current refined analysis by cell type and treatment may reveal significant differences. Two centers, Kansas and Connecticut, have completed manuscripts on the queries that each center added to the interview qestionnaire. In Kansas, the issue was insurability. The 101 survivors, who met the additional design criteria (no evidence of cancer and at least one same-sex sibling) had more difficulty in securing life and health insurance and had lower amounts of life insurance coverage, than sibling controls. In Connecticut, the issue was socioeconomic achievements and major depression episodes. The 450 cases

compared to 587 siblings, had equal frequencies of major depressions (although more females were depressed than males, 23% and 12-15%, respectively). Male and female survivors were more often rejected from military duty, but males only were more often denied jobs or college admission.

2) Manuscript preparation is nearly complete on a registry of 133 pregnancies in 66 young women with cancer, assembled from physicians participating in Cancer and Acute Leukemia Group B. Present analysis showed little, if any, teratologic effect, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy.

3) Review articles were prepared to emphasize the principles of mutation epidemiology and the potential usefulness of studies of reproduction by cancer patients in addressing the refractory question about human germinal mutagens.

A workshop was organized and held in Oslo in May 1985, to explore European interest in coordinating collection of additional data, since pregnancy in cancer patients is still a rare event. Planning meetings were held in preparation for a NCI-sponsored International Conference on Reproduction in Human Cancer to be convened in Spring 1986, and published as a monograph.

Significance to Biomedical Research and the Program of the Institute:

The study of reproduction in cancer patients may help document the familiality of certain tumors, especially of childhood, the predicted but poorly documented teratogenicity of modern cancer therapy, and the predicted but undocumented germinal mutagenicity of radiation and drugs. The data may be directly used in counseling cancer patients.

Proposed Course:

The case registry of Cancer and Acute Leukemia Group B is closed. The five center study is in intensive analysis, with a series of planned publications. Additional populations suitable for investigation are being identified, as well as the feasibility of laboratory measures of mutation, to increase the statistical power of subsequent studies.

Publications

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

Mulvihill, J.J.: Offspring of long-time survivors of childhood cancer. Semin. Oncol. (In Press)

Mulvihill, J. J.: Reproduction in cancer patients. In Ramel, C. (Ed.): Proceedings of the Fourth International Conference on Environmental Mutagens. New York, Alan R. Liss. (In Press)

Mulvihill, J. J. and Czeizel, A.: Perspectives of mutation epidemiology. 6: A 1983 view of sentinel phenotypes. Biol. Zentralbl. (In Press)

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05194-04 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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
	R. E. Tarone	Biostatistician	BB	NCI
	P. H. Levine	Senior Investigator	CEB	NCI
	C. E. Land	Biostatistician	EEB	NCI

COOPERATING UNITS *(if any)*

National Center for Health Statistics (R. Israel)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

R. W. Miller	Chief	CEB	NCI
F. W. McKay	Computer Systems Analyst	CEB	NCI
R. E. Tarone	Biostatistician	BB	NCI
P. H. Levine	Medical Officer	CEB	NCI
C. E. Land	Biostatistician	EEB	NCI

Objectives:

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

2. To project the numbers of cancer cases expected in the next 20 years based on changes in the age distribution of the population; e.g., the baby boom of the 1950s.

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

Methods Employed:

The data, which were collected by the National Center for Health Statistics (NCHS) in a varying format from year to year, 1950-1981, have been reworked into a common format. The widely known Atlases of Cancer Mortality in the U.S. by County were the first results from studying these data. Programs have now been developed for creating three-dimensional graphs of cancer mortality rates by site, race, sex, calendar year and age-group. The graphs are drawn on a Calcomp X-Y plotter.

The most efficient use of computer time has been achieved through the use of programs written in COBOL, Fortran or Assembler. Over 30 fast-running programs are used to keep the data base current. Most programs are run often enough to keep their operation efficient.

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

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

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

Significance to Biomedical Research and the Program of the Institute:

The computer-generated volumes of tables and graphs of national cancer mortality are widely used, and special requests are frequently received and information provided.

Proposed Course:

Continue to use and improve this resource.

Publications

Miller, R. W.: Aetiology and epidemiology [of childhood cancer]. In Barrett, A. and Voute, P. A. (Eds.): Cancer in Children, Clinical Management. New York, Springer-Verlog, 1985. (In Press)

Miller, R. W.: Chemical Pollutant. In Behrman, R. E. and Vaughan, V. C., III (Eds.): Nelson's Textbook of Pediatrics. 14th edition. Philadelphia, W. B. Saunders, Co. (In Press)

Miller, R. W.: Congenital PCB poisoning: A reevaluation. Environ. Health Perspect. (In Press)

Miller, R. W.: Detection of environmental effects through anatomic pathology. In Scarpelli, D. G. and Craighead, J. E. (Eds.): The Pathologist and the Environment. Baltimore, MD, Williams and Wilkins. (In Press)

Miller, R. W.: Effects of prenatal exposure to ionizing radiation. In: Some Issues Important in Developing Basic Radiation Protection Recommendations. NCRP Publication No. 6. Bethesda, MD, National Council on Radiation Protection and Measurements, 1985, pp. 62-71.

Miller, R. W.: Genetic and familial factors. In Calabresi, P., Schein, P. S., and Rosenberg, S. A. (Eds.): Medical Oncology. New York, MacMillan Publishing Co., Inc. (In Press)

Miller, R. W.: Introductory remarks: Biostatistics in cancer research. Environ. Health Perspect. (In Press)

Miller, R. W.: Radiation Injury. In Behrman, R. E. and Vaughan, V. C., III (Eds.): Nelson's Textbook of Pediatrics. 14th edition. Philadelphia, W. B. Saunders, Co. (In Press)

Miller, R. W.: Some persons at high risk of lymphoproliferative diseases. In McGrath, I., O'Conor, G., and Ramot, B. (Eds.): Pathogenesis of Leukemias and Lymphoma. Environmental Influences. New York, Raven Press, 1984, pp. 201-206.

Miller, R. W. and Boice, J. D. Jr.: Radiogenic cancer after prenatal or childhood exposure. In Upton, A. C. and Shore, R. E., (Eds.): Radiation Carcinogenesis. New York, Elsevier-North Holland. (In Press)

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

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05279-03 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Development of Epidemiologic Data Resources

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

PI:	G. W. Beebe	Statistician (Health)	CEB	NCI
Others:	R. Spirtas	Biostatistician	EEB	NCI
	J. D. Boice	Chief	REB	NCI
	E. Pollack	Chief, BB	DCPC	NCI
	T. J. Mason	Chief, PSS	EEB	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

G. W. Beebe — Health Statistician — CEB NCI

Objectives:

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

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

Methods Employed:

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

Major Findings:

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

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

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

4. Through the NIH/Census/NDI Working Group it was determined that the linking of a significant part (4.5 million) of the 1980 Census with the National Death Index (NDI) to create mortality tables in relation to industry, occupation, and other demographic, geographic, and economic facts entered on the Census "long form" was possible by computer, but that without the Social Security number (SSN) on the Census return the completeness of mortality ascertainment would probably never reach 90 percent. This work also showed that the current algorithm used by the NDI would probably match correctly only about 80 percent of deaths in the absence of the SSN. The basis was laid for a more effective matching algorithm in the future. Present efforts focus on the Current Population Survey (CPS) as a substitute for the 1980 Census sample. Census has put together a sample of about 900,000 CPS subjects of past surveys in which the SSN was obtained. This sample is too small for NCI purposes.

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

6. Although Health Care Financing Administration (HCFA) has cooperated with NCI in the past, providing addresses for individuals whom NCI investigators needed to locate, and samples of individuals in specific areas who might be used as controls, it had not been possible to obtain addresses from SSA. The need for addresses for the hepatitis follow-up study provided a means of probing SSA policy as to the disclosure of SSA addresses and also SSNs and after considerable negotiation and the intervention of Dr. Brandt, then Assistant Secretary for Health, it was possible to conclude agreements with SSA under which such information has been provided. It is still not clear, however, that SSA's conditions can be met for using SSNs obtained from SSA to procure addresses from IRS through NIOSH.

Significance to Biomedical Research and the Program of the Institute:

The work on epidemiology data sources, which is organized through the NCI Working Group on Epidemiology Data Sources, holds promise for developing better research tools and opportunities for epidemiologic research, for pointing to differential risks that may deserve more intensive study, for monitoring changes in carcinogenic risk at the mortality level, and for judging the impact of preventive programs in industry.

Proposed Course:

The search for neglected data bases will be continued. With the start that has been made in the area of occupational mortality, it is expected that one or another of the various approaches to the development of a national system will in time succeed. Efforts will be continued to develop all the apparent options for creating this information: systematic coding of the information on the death certificate; the CWHS with or without information on occupation, or perhaps an even larger sample of Social Security account numbers; and linkage of the Current Population Survey to the National Death Index. Efforts will be continued to ease restrictions on the access of health researchers to major Government files, such

as the IRS address list and the Social Security records of employees by industry of employment.

Publications

Beebe, G. W.: Record linkage: Methodologic and legal issues. Arch. Environ. Health 39: 169-172, 1984.

Beebe, G.W.: Why Are Epidemiologists Interested in Matching Algorithms? Proceedings of Workshop on Exact Matching Methodologies, May, 1985. Washington Statistical Society and the Federal Committee on Statistical Methodology. (In Press)

Kurtzke, J. F., Beebe, G. W. and Norman, J. E., Jr.: Epidemiology of multiple sclerosis in US veterans. 3. Migration and the risk of MS. Neurol. 35: 672-678, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05280-03 CEB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

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

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Epidemiology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

A-bomb survivors, Atomic Energy Commission--Department of Energy workers, the population exposed to fallout from atmospheric tests at the Nevada Test Site, etc., have been studied for their potential to provide low-dose risk estimates for radiogenic cancer. Only some combination of experimental and theoretical work, with epidemiologic studies at higher doses, will provide a reliable guide to such risks. Sources of variation in risk estimates for radiogenic cancer are explored for their significance to research on carcinogenic mechanisms and to give direction to epidemiologic research.

PROJECT DESCRIPTION

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

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

Objectives:

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

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

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

Methods Employed:

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

Major Findings:

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

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

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

4. At the request of the organizer of the symposium, Dr. Beebe was invited to participate in the Symposium on the Estimation of Human Carcinogenic Risks at the meeting of the Radiation Research Society in May, 1985. His topic was "Recent Developments in Human Risk."

Significance to Biomedical Research and the Program of the Institute:

The work on carcinogenic effects of ionizing radiation provides up-to-date descriptive information on empirical risks, direction for epidemiologic research efforts, a factual basis for regulatory standards, and a stimulus to thinking about the underlying biologic meaning of observed risk differentials in the human data.

Proposed Course:

The analysis of radiogenic cancer risk estimates will be continued, with special attention to differential risks associated with host factors, other environmental risk factors, specific tissues and organs, time from exposure, and such characteristics of radiation as its quality and dose-rate.

Publications

Beebe, G.W.: Hiroshima-Nagasaki: The balance sheet after 40 years. In Galle, P., Masse, R., and Nenot, J.-C. (Eds.): Irradiations Accidentelles et Therapeutiques. Creteil, France, Faculte de Medecine, 1984, pp. 2-26.

Beebe, G. W.: The RERF research agenda for studies of radiation-induced cancer. In Prentice, R. L. and Thompson, D. J. (Eds.): Atomic Bomb Survivor Data: Utilization and Analysis. Philadelphia, Society for Industry and Applied Mathematics, 1984, pp. 251-273.

Boice, J. D., Jr., Beebe, G. W., and Land, C. E.: Absolute and relative time-response models in radiation risk estimation. In Proceedings of the 20th Annual Meeting of the National Council on Radiation Protection and Measurements. Bethesda, MD, National Council on Radiation Protection and Measurements, 1985, pp. 22-50.

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

Neel, J. V., Miller, R. W., and Beebe, G. W.: Delayed effects from the exposure of the Japanese to Atomic Bombs. Bull. Atomic Scientists. (In Press)

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

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05319-02 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Epidemiologic Studies on Viruses and Genetics in the Etiology of Cancer

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

PI:	Paul H. Levine	Senior Investigator	CEB	NCI
Others:	R. W. Biggar	Senior Investigator	EEB	NCI
	D. V. Ablashi	Microbiologist	LCMB	NCI
	C. Saxinger	Senior Investigator	LTCB	NCI

COOPERATING UNITS *(if any)* Institut Salah Azaiz, Tunis, Tunisia (N. Mourali); Univ. Malaya, Kuala Lumpur, Malaysia (U. Prasad); Univ. of Ghana, Accra, Ghana (F. Nkrumah); George Washington University, Washington, D.C. (P. Seraganian and C. Alter); Institute for Cancer Research, Aarhus, Denmark (M. Melbye and P. Ebbesen)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	0.0

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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

This project uses a variety of epidemiologic techniques in conjunction with collaborating laboratories to investigate the relative role of viruses and genetics in human virus-associated tumors. Emphasis is placed on the intensive study of tumors occurring in unusual situations suggestive of an environmental etiologic factor. Evaluation of the immune response to specific candidate oncogenic agents and a search for chromosomal or other genetic markers are performed in an attempt to determine whether genetics affects the response to ubiquitous viruses in the appearance of malignancy. Among the findings in these studies are the following: antibody to HTLV-III was detected in 50 of 75 serum samples collected in Uganda in 1972-73 providing strong evidence that sub-Saharan Africa is the origin of the AIDS virus; analysis of data provided by the Surveillance, Epidemiology and End Results Program (SEER) indicated that the incidence of Burkitt's lymphoma (BL) appears to be increasing in young white males in the United States and that inflammatory breast cancer (IBC) defined clinically may be a distinct entity from pathologically defined IBC; hormone receptor studies support the hypothesis that rapidly progressing breast cancer (RPBC), as determined by patient history, is the same entity as RPBC with objective signs of redness, warmth and edema. A geographic cluster of nasopharyngeal carcinoma (NPC) and BL, two neoplasms associated with the Epstein-Barr virus (EBV), was identified in a three-county area in Texas; a study of Greenland Eskimos and Danes demonstrated that early primary infection with EBV correlated with risk of developing NPC.

PROJECT DESCRIPTION

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

P. H. Levine	Senior Investigator	CEB NCI
R. W. Biggar	Senior Investigator	EEB NCI
D.V. Ablashi	Microbiologist	LCMB NCI
C. Saxinger	Senior Investigator	LTCB NCI

Objectives:

To identify specific individuals, families, or populations which provide evidence for an etiologic role of viruses in the appearance of cancer. Laboratory tests are applied to search for specific candidate oncogenic viruses and, in addition, a battery of assays searching for genetic markers of susceptibility to cancer are applied.

Methods Employed:

Individuals in multiple case cancer families or individuals with cancer occurring under unusual circumstances or after unusual exposures are identified by attendance on ward rounds, at clinical meetings, or on referral. Populations of individuals at high risk of developing cancer or with unusual forms of cancer are identified by collaborating investigators in Tunisia, Malaysia, Denmark, Ghana, and other parts of the world. Serum samples, tumors, and other relevant biologic specimens are stored at the Tumor Virus Epidemiology Repository, which is located at the Frederick Cancer Research Facility in Frederick, Maryland, and are distributed to collaborating laboratories with appropriate assays to detect specific viral or genetic markers.

Major Findings:

1. Higher frequencies of HTLV-I and -III were found in Uganda than in the rest of Africa. An intermediate rate of infection was found in Ghana. The sera used for the study were part of the collection of the Tumor Virus Epidemiology Repository in Frederick, Maryland. The frequency of HTLV-III, 67% in sera from Uganda collected before 1973, is evidence that Africa is the source of this virus, which is the probable etiologic agent of AIDS. The infection in Africa may be asymptomatic, may involve less pathogenic strains than those that induce AIDS, and/or may encounter resistance in populations that have long been exposed. Another possibility is that the infection is less pathogenic when it is not transmitted by homosexual contact or injection.

2. Family studies revealed striking occurrences of breast cancer in two black families and a Fanconi-like anemia in a father, his brother and two daughters, one of whom also developed acute myelomonocytic leukemia. Laboratory studies were undertaken to clarify the pathobiology of these occurrences and to attempt to determine the risk of disease in currently unaffected family members.

3. Hormonal studies in Tunisian breast cancer patients indicated a similarity between rapidly progressing breast cancer (RPBC) in Tunisia and inflammatory

breast cancer (IBC) in the United States. An evaluation of the SEER data on IBC in the United States indicated that pathologic identification of inflammatory breast cancer has a greater prognostic impact than the clinical description of IBC.

4. Seroepidemiologic studies showed that Danish children and adults in Greenland, an area with an increased incidence of nasopharyngeal carcinoma, have higher antibody titers to Epstein-Barr virus than Danes remaining in Denmark.

5. To determine the representative nature of the American Burkitt's Lymphoma Registry, population-based data on American Burkitt's lymphoma were collected from the Surveillance, Epidemiology and End Results (SEER) Program and national mortality data. Among the findings from these data were: 1) the first approximation of incidence rates in the United States (1.4/million for males and 0.4/million for females), the group most at risk being males at ages 0-14 with a rate of 3/million; 2) the documentation of a marked preponderance of BL in young males (incidence and mortality data reflecting a 6:1 male:female ratio under age 14 years); 3) the confirmation of the relative underrepresentation of blacks in the American BL population; and 4) the confirmation of the findings of the ABLR as to the curability of BL for patients with a disease-free status of at least two years following chemotherapy.

6. Among the investigations of cancer occurring in unusual circumstances, one study involved a cluster of three young patients with nasopharyngeal carcinoma and three with BL occurring in a three-county area in Texas. This was the first report of geographic clustering of these two EBV-related diseases.

Significance to Biomedical Research and the Program of the Institute:

Genetic susceptibility to oncogenic viruses in individuals, families, and/or populations and the interaction of environmental factors and genetics can be studied in depth by new laboratory techniques. This project has provided information and clinical specimens useful in studying the pathogenesis of cancer. Breast cancer is one of the most common tumors of women worldwide and is a significant public health problem in the United States. The development of a strong collaborative effort between the National Cancer Institute and the Institut Salah Azaiz in Tunisia is of great value in that it provides access to a group of patients with rapidly progressing breast cancer (RPBC). The high frequency of RPBC in Tunisia allows information on this entity to be accumulated more rapidly than in the United States. Clinical and pathological data thus far indicate that RPBC in Tunisia is no different than fulminating breast cancer in the United States and, therefore, information obtained from the Tunisian patients would be directly applicable to breast cancer patients in the United States. The finding in breast cancer of the high content of antigen cross-reacting with MMTV indicates that human material will be available that will accelerate studies on the involvement of viruses in the cause of breast cancer. The chemotherapy studies have already been of value to breast cancer patients in the United States and the results of these studies are encouraging American chemotherapists to treat patients with RPBC who in the past had not been treated with chemotherapy. The immunologic studies demonstrate the integrity of the immune system in patients with RPBC, providing guidelines to management of such patients.

Continued development of the Tumor Virus Epidemiology Repository (TVER) is assisting in the application of newer laboratory techniques to studies of the genetic susceptibility to viruses in individuals, families, and/or populations at risk of developing cancer. Initially developed for the study of the role of Epstein-Barr virus in the etiology of Burkitt's lymphoma in Ghana, the TVER is also being applied to studies on the role of HTLV in the etiology of T-cell leukemia and EBV in the etiology of NPC. Should other candidate oncogenic viruses be identified, the TVER will be of great value in epidemiologic studies of such viruses in different parts of the world.

Proposed Course:

A follow-up of BL patients identified through the ABLR will investigate the possible familiality of BL and examine whether the epidemiologic features of EBV-associated BL in the United States differ from non-EBV associated BL. The collection of sera and tumors from American BL patients is expected to add to current knowledge regarding the uniformity and significance of the 8;14 translocation in this disease as well as the presence of oncogenes in the tumor.

In addition to ongoing studies in NPC, new projects will concentrate on two areas: the role of genetics in the etiology of NPC and the assessment of the heterogeneity of NPC. Genetic studies will include the identification of familial NPC in Chinese living in Canton, Fukkien, Malaysia and Singapore, and the search for specific chromosomal abnormalities in tumors obtained from NPC patients. Studies on the heterogeneity of NPC will emphasize the collection of paraffin blocks from cohorts in different parts of the world to address the question of whether NPC is two diseases--EBV-associated undifferentiated NPC and keratinizing non-EBV-associated NPC--or whether there is a spectrum perhaps affected by degree of host response. The observation of elevated EBV titers in Greenland Danes will be pursued by longitudinal follow-up of Danish migrants to Greenland for serologic changes and subsequent incidence of NPC.

The TVER will expand its collection of specimens to include NPC cases and controls from Malaysia and BL cases and controls from Tunisia. A new effort in the Repository, based on advances in the immunodetection of a variety of antigens in formalin-fixed tissue, will be to develop a repository of slides from NPC and breast-cancer patient studies which will be available for other immunoepidemiologic studies as reagents become available.

The studies in breast cancer will be continued with a more in-depth epidemiologic study of the risk factors for aggressiveness associated with the disease in Tunisia. Findings from this study will be applied to a comparable study of inflammatory breast cancer in the United States. An immunoperoxidase study will be applied to a series of breast cancer patients in the United States and other countries in order to further determine the etiologic and prognostic significance of this antigen in breast cancer. More sensitive antibodies will be applied to the study of familial breast cancer to possibly identify the individuals in breast cancer families who might be at high risk of developing breast cancer.

Publications

Bale, S. J., Bale, A. E., and Levine, P. H.: The "family study" approach to investigating the role of genetic factors in nasopharyngeal carcinoma. In Levine, P. H., Ablashi, D. V., Pearson, G. R., and Kottaridis, S. (Eds.): The Epstein-Barr Virus and Associated Malignancies. Boston, Martinus Nijhoff. (In Press)

Biggar, R. J., Saxinger, C., Gardiner, C., Collins, W. E., Levine, P. H., Clark, J., Nkrumah, R., and Blattner, W.: Type-1 HTLV Antibody in Urban and Rural Ghana, West Africa. Int. J. Cancer 34: 215-219, 1984.

Boss, L. P., Levine, P. H., and Hanes, R. S.: A Cluster of Young Patients with Burkitt's Lymphoma and Nasopharyngeal Carcinoma in Central Texas. JAMA 253: 2843-2846, 1985.

Levine, P. H.: The Epidemiology of Epstein-Barr Virus-Associated malignancies. In Levine, P.H., Ablashi, D. V., Pearson, G. R., and Kottaridis, S. (Eds.): The Epstein-Barr Virus and Associated Malignancies. Boston, Martinus Nijhoff. (In Press)

Levine, P. H., Ablashi, D. V., Pearson, G. R., and Kottaridis, S. (Eds.): The Epstein-Barr Virus and Associated Malignancies. Boston, Martinus Nijhoff. (In Press)

Levine, P. H. and Connelly, R. R.: Epidemiology of nasopharyngeal cancer. In Wittes, R. E. (Ed.): Head and Neck Cancer. Sussex, U.K., John Wiley & Sons Ltd., 1985, pp. 13-34.

Levine, P. H., Connelly, R. R., and McKay, F. W.: Burkitt's lymphoma in the United States: Cases reported to the American Burkitt Lymphoma Registry compared with population-based incidence and mortality data. In Lenoir, G., O'Conor, G. T., and Olweny, C. (Eds.): Burkitt's Lymphoma: A Human Cancer Model. (In Press)

Levine, P. H., Steinhorn, S. C., Ries, L. G., and Aron, J. L.: Inflammatory Breast Cancer: The Surveillance, Epidemiology and End Results (SEER) Experience. JNCI. 74: 291-297, 1985.

Levine, P. H., Tabbane, F., Muenz, L. R., Kamaraju, L. S., Das, S., Polivy, S., Belhassen, S., Scholl, S.M., Bekesi, J. G., and Mourali, N.: Hormone receptors in rapidly progressing breast cancer. Cancer 54: 3012-3016, 1984.

Melbye, M., Ebbesen, P., Levine, P. H., and Bennike, T.: Early Primary Infection and High Epstein-Barr Virus Antibody Titers in Greenland Eskimos at High Risk for Nasopharyngeal Carcinoma. Int. J. Cancer 34: 619-623, 1984.

Nkrumah, F. K., Pizza, G., Viza, D., Neequaye, J., De Vinci, C., and Levine, P. H.: EBV-specific transfer factor in the treatment of African Burkitt's lymphoma: A pilot study. In Levine, P. H., Ablashi, D. V., Pearson, G. R., and Kottaridis, S. (Eds.): The Epstein-Barr Virus and Associated Malignancies. Boston, Martinus Nijhoff. (In Press)

Nkrumah, F., Pizza, G., Viza, D., DeVinci, C., and Levine, P.: Regression of Progressive Lymphadenopathy in a Young Child with Acute Cytomegalovirus (CMV) Infection following the Administration of Transfer Factor with Specific Anti-CMV Activity. Lumphokine Res. (In Press)

Saxinger, W., Blattner, W. A., Levine, Ph. H., Clark, J., Biggar, R., Hoh, M. W., Moghissi, J., Mourali, N., Nkrumah, F. K., WIlson, P. J. L., Jacobson, R., Crookes, R., Strong, M., Ansari, A. A., and Gallo, R. C.: Human T-Cell Leukemia Virus (HTLV-1) Antibodies in Africa. Science 225: 1473-1476, 1984.

Saxinger, C., Lange-Wantzin, G., Levine, P. H., Dean, A., and Gallo, R.: Unique Pattern of HTLV-III (AIDS-related) Antigen Recognition by Sera from African Children: Uganda (1972). Cancer Res. (In Press)

Saxinger, W. C., Levine, P. H., Dean, A. G., de The, G., Lange-Wantzin, G., Laurent, F., Moghissi, J., Hoh, M., Sarngadharan, M. G., and Gallo, R. C.: Evidence for Exposure to HTLV-III in Uganda before 1973. Science. 227: 1036-1038, 1985.

Sundar, S. K., Levine, Ph H., Ablashi, D. V., and Menezes, J.: Retinoic Acid and Steroids Inhibit Epstein-Barr Virus-Induced Nuclear Antigen, DNA Synthesis and Lymphocyte Transformation. Anticancer Res. 4: 415-418, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05329-02 CEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Hepatitis B Virus and Liver Cancer in Army Veterans of WWII

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

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

COOPERATING UNITS *(if any)*

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

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☒ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

G. W. Beebe Statistician (Health) CEB NCI

Objectives:

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

Methods Employed:

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

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

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

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

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

Major Findings:

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

Significance to Biomedical Research and the Program of the Institute:

Although many lines of evidence associate HBV with PHC, especially in Asia and Africa, there is great uncertainty as to 1) the probability that a single adult exposure will induce the chronic carrier state thought to lead to liver cancer, 2) the persistence of the carrier state, and 3) the role of cirrhosis in the pathogenesis of liver cancer. In addition, the long-term natural history of viral hepatitis remains ill-defined, especially with reference to the likelihood of chronic hepatitis and cirrhosis.

This study should make a positive contribution to the viral etiology of cancer as illustrated by the relationship between HBV and PHC. It should also further our knowledge of the natural history of HBV generally.

Proposed Course:

As outlined above.

Publications

None; one scientific presentation of preliminary serologic results.

ANNUAL REPORT OF

THE ENVIRONMENTAL EPIDEMIOLOGY BRANCH

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

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.

For the second year in a row, a major change directly affecting the EEB occurred within the Epidemiology and Biostatistics Program. Specifically, as part of a reorganization and upgrading of the Biostatistics Branch (BB) within the Program, the entire Analytical Studies Section from the EEB was transferred to become a Section within the BB. Dr. William Blot remained as Section Chief and also was named the Chief of the Biostatistics Branch. Other departures from the Branch included Drs. David Tollerud and Arlene Kantor, both of whom completed their Staff Fellowships. Ms. Marian Heid retired from Federal service after a number of years working as a nosologist for NCI and NIOSH, and Dr. Mark Greene, Deputy Branch Chief, left to enter the private practice of oncology.

Joining the Occupational Studies Section within the past year in a cancer expert position was Dr. Richard Hayes. Dr. Hayes is an epidemiologist with seven years of experience beyond his doctoral degree, mostly in the conduct of cancer epidemiology in the Netherlands. A number of students have also been working on projects within the Branch over the past year. Ms. Janet Stanford and Ms. Audrey Saftlas of Johns Hopkins University worked on their doctoral thesis topics as guest researchers. Ms. Karen Tashima, a medical student from Columbia University, and Ms. Denise Riedel, a public health student from Yale University, were selected for the summer fellowship program. Dr. Mads Melbye, a physician-epidemiologist from Denmark, joined the program as a visiting researcher to pursue more intensively a continuing series of studies of AIDS.

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 programs of study focused in particular areas.

Descriptive Studies: To identify systematically geographic variation in clustering of cancer mortality, the Branch has analyzed U.S. cancer mortality on a county level. In the past, cancer death rates were developed and published along with maps illustrating the variation. Relating these patterns to demographic and potential exposure information, that were also characterized at the county level through correlational or hypothesis-generating studies, often led to a series of hypotheses about the reasons for observed cancer patterns.

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

Field Studies in High-Risk Areas: A substantial proportion of field studies in high-risk areas of the U.S. and the rest of the world have been the responsibility of members of the Analytical Studies Section, which was part of the EEB for approximately one half of this fiscal year and was transferred to the Biostatistics Branch for the remainder of the year. For this reason, a more extensive discussion of this particular program area is contained in the Annual Report of the Biostatistics Branch. In brief, within the U.S. there was some activity within the past year on a variety of case-control studies involving lung cancer in New Jersey, coastal Texas, and Louisiana; renal cell and renal pelvis malignancies in Minnesota; bladder cancer in rural New England; esophageal cancer in coastal South Carolina; nasal cancer in North Carolina and Virginia; and stomach and pancreatic cancer in southern Louisiana. Internationally, case-control studies of cancers of the esophagus, stomach, lung, and choriocarcinoma were begun in areas of China at high risk for these tumors, while a case-control study of gastric cancer was initiated in high-risk areas of Italy.

Highlights of results from some of these studies include identification of ethnic factors, cigarette smoking, and (among women) high relative weight as a risk factors for renal adenocarcinoma. Cigarette smoking and long-term use of certain analgesics were identified as risk factors for renal pelvis cancer. While data from the lung cancer studies are still being analyzed, a number of high-risk occupations, including work in shipyards and the construction industry, have thus far been identified. Much of the excess risk of bladder cancer in rural New England seems to be attributable to prior work in the leather and textile industries. Risk factors for nasal cancer include exposure to wood dust for adenocarcinoma and cigarette smoking for squamous-cell malignancies.

Descriptive observations throughout the U.S. and elsewhere are continually evaluated for high-risk areas where analytic studies might be expected to yield clues to etiology of the tumors that occur excessively. Most recently, a multi-center, case-control study of cancer of the uterine cervix has been initiated in Latin America to elucidate reasons for the very high rates in this part of the world. A particular focus of this study will be the role of the so-called "male risk factor" among sexual partners of cases.

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.

Several different proportional mortality studies and death certificate-based case-control studies were performed in order to generate hypotheses about occupational causes of malignancy which could be tested more robustly in subsequent analytic studies. A proportional mortality study of embalmers exposed to formaldehyde and other fixatives revealed an excess of leukemia and cancer of the brain. Proportional mortality evaluation of professional artists exposed to paints and solvents revealed an excess risk of leukemia and bladder cancer. Using death certificates, case-control studies of prostate and colon cancers failed to find any excess risk associated with work in the textile industry, an association suggested by other reports. A death certificate-based case-control study of chronic lymphatic leukemia indicated an excess risk among farmers, particularly in areas associated with cattle production, while excess risks of myeloid leukemia tended to be associated with farming in areas where corn, hog, and chicken production, along with pesticide and fertilizer use, were high.

The large nation-wide cohort study of close to 300,000 veterans, which had been conducted to evaluate the risk associated with tobacco use, was re-analyzed to assess risks associated with the reported occupation and industry of the subjects. The information on tobacco use allowed appropriate control for this potential confounding variable in a hypothesis-generating case-control evaluation. Excesses of lung cancer were noted among shipyard workers, truck drivers, and railroad workers. A provocative pattern of elevated risks for stomach cancer was noted among carpenters, machinists, and steelworkers, and may reflect exposure to dusts and abrasives.

A number of analytic case-control and cohort investigations were also conducted to test a variety of hypotheses. In one investigation of bladder cancer in New England, a 50 percent excess risk was noted among truck drivers. This risk rose to over two-fold for those employed five or more years, thus confirming an earlier study of the Branch implicating automobile emissions

as a potential risk factor. In another study of bladder cancer, a three-fold excess risk was found among professional artists, which was duration-related and was not altered by control for cigarette smoking. This confirmed the earlier lead noted by the proportional mortality study.

An evaluation of a screening program among pattern makers for colorectal cancer and polyps, developed after the identification of an excess risk of colon cancer in this group, uncovered a 2.5-fold excess risk of colon cancer. Further analyses were unable to link the excess to any specific characteristic of pattern making.

In a collaborative venture with several national Swedish agencies, record-linkage studies in this country were performed linking cancer incidence data with information on occupation and industry. These studies detected a relationship between the risk of mesothelioma and occupation including mechanics, plumbers, painters, pulp workers, tire workers, and workers in the shipbuilding and railroad equipment industry, as well as in the sugar refinery industry. In addition, an excess risk of kidney cancer was linked to work in the leather industry.

Several large analytic investigations completed field operations in the past year and are currently being analyzed. This includes a large-scale cohort investigation of workers exposed to formaldehyde in five separate industries in which approximately 30,000 exposed workers and over 4,000 deaths are being related to job title and the level of exposure. Also under analysis are two studies of non-Hodgkin's lymphoma, one of adult leukemia, and one of soft-tissue sarcoma, all in areas with an extensive agricultural industry. Analyses are focusing on the reasons for excesses of lymphoma and leukemia among farmers, as well as suggestions that lymphomas and soft-tissue sarcomas may be related to specific pesticide exposures.

A number of other analytic investigations continue in the field. Included are case-control investigations of brain tumors in geographic locations where the petrochemical industry is concentrated, case-control evaluations of risk factors for mesothelioma, and cohort studies of a large group of airplane maintenance workers and an industry-based study of acrylonitrile. This year staff scientists also reviewed important current topics in occupational cancer including formaldehyde, silica and other nonorganic dusts, and herbicides for publication or presentation at scientific meetings or to the Congress, or to regulatory and other review bodies.

Medicinal Agents: The Branch conducts a variety of studies to assess drug-induced cancer. The rationale for this is two-fold. Such studies have been valuable in the discovery of previously unrecognized carcinogenic hazards, and they have allowed insights into mechanisms of carcinogenesis. This has been so, not necessarily because of the presence of a large burden of drug-induced cancer in our society, but rather because drug exposure

usually involves high doses which can be assessed by standard epidemiologic approaches. In conducting this program, epidemiologic, clinical, and laboratory observations are monitored for candidate drugs that can be evaluated for carcinogenic effects utilizing special resources developed by the Branch. These resources include the monitoring of clinical trials for long-term effects, follow-up of specific patient populations, intensive case-control investigations, and record-linkage studies within prepaid health plans. In recent years, the focus of this program has been primarily on hormonal medications and cytotoxic drugs, although a variety of other agents have also been evaluated.

Analysis of a large case-control study of breast cancer done within the context of a mammography screening project revealed no excess risks associated with the use of thyroid or anti-hypertensive medications. However, women with untreated hypothyroidism or goiter had a significantly reduced risk of breast cancer. In addition, while there was no overall excess, long-term users of rauwolfia compounds for the treatment of hypertension did appear to experience some elevation in risk. Analysis of the relationship of estrogen replacement therapy and the risk of benign breast disease diagnosed within this screening program revealed an excess risk that was related to duration of estrogen use, rising to approximately two-fold among those who had used estrogens for 15 years or longer. Analyses of two separate case-control studies of cancer of the uterine cervix have revealed a significant excess risk associated with the use of oral contraceptives which appears to be related to duration of use. Those who have used oral contraceptives for 5 or more years have a two-fold risk of cervical cancer, after controlling for all other relevant confounding factors.

Preliminary analyses of a medical record review case-control study of ovarian cancer in prepaid health plans revealed no relationship with the use of exogenous estrogens, a slight protective effect associated with oral contraceptive use, and the suggestion of an increased risk either with the use of progestational drugs or with the indication for which such drugs were used (primarily abnormal uterine bleeding at ages 40 or greater). In addition, analysis of data from a large population-based study of bladder cancer revealed no excess risk associated with medications used for tuberculosis treatment or prophylaxis.

The Branch has continued its program to evaluate the potential carcinogenicity of the various cytotoxic agents used in the treatment of cancer and some non-neoplastic conditions. Follow-up studies of patients treated for ovarian cancer, gastrointestinal cancer, brain cancer, trophoblastic neoplasms, and Hodgkin's disease have either been completed or are currently underway. Thus far these studies have revealed excess risks associated with a number of different alkylating agents and two different nitrosoureas. All of these associations show evidence of dose-response relationships. In addition, it appears as though melphalan is 3.5 times more likely to cause leukemia than is cyclophosphamide. Thus far no excess risk of second primary neoplasms has been related to treatment with anti-metabolites. A case-control study of

second primary neoplasms in children treated for childhood malignancy revealed a leukemia excess which was unrelated to radiation therapy but related in a dose-response manner to the total amount of alkylating agents administered. More recent analyses of these data have suggested that second primary bone cancers may be related to both radiation treatment and alkylating agent exposure. Current emphasis is being placed on analytic evaluations of cytotoxic drugs used as adjuvant therapy, particularly for breast cancer. These studies include long-term follow-up of randomized clinical trials, as well as a case-control study of second primary leukemias occurring in women with breast cancer.

Of special interest is the assessment of *in utero* exposure to drugs among individuals who developed brain tumors in childhood or testicular malignancies as young adults. In addition, more detailed pursuit of the relationship between hormonal agents and breast neoplasia is being conducted in prepaid health plans to simultaneously assess the pathology of lesions, hormone treatment, and risk of benign disorders and malignant neoplasia.

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. Initially, these efforts involved the addition of a nutritional component to studies being conducted mainly for other reasons. In this manner, dietary factors were sought in case-control evaluations of oral cancer among women in North Carolina and of lung cancer in several high-risk areas. A dietary component was also incorporated into investigations of the excesses of pancreatic and stomach cancers in southern Louisiana. The case-control study of oral cancer suggested that consumption of fruit and vegetables was consistently low in the diet of the cases. The relative risk of stomach cancer in the high-risk area of southern Louisiana was inversely related to an index of vitamin C intake. Analyses of the lung cancer investigations appear to show a consistent pattern of lower risks associated with higher levels of consumption of fruit and vegetables, but no consistent relationship with estimates of retinol intake. In the most extensively analyzed study (New Jersey), the relationship is limited to squamous-cell tumors and is most prominent in current smokers.

Recently, the Branch completed the field phase of a large case-control study of invasive and *in situ* cervical cancer to assess a variety of risk factors. The nutritional aspect to this study measures the intake of various micronutrients, both by interview about usual adult dietary patterns and by laboratory assays of samples, and is currently under analysis.

With the experience gained through incorporation of nutritional elements in other studies, we have recently initiated studies whose major rationale is dietary assessment. A collaborative study with the three population-based cancer registries in areas covering substantial Asian-American populations is focusing on diet, particularly at a young age, and its relation to breast cancer risk among Asian-Americans. The study also involves measurements of

hormones and macro- and micronutrients in biological specimens. Another study under analysis seeks to evaluate a suggestion from geographic studies of colorectal cancer that the risk among migrants from high-risk northern areas of the U.S. to low-risk retirement areas in the south declines rapidly to the low southern rate. Initial analysis seems to indicate that age at such migration is key, with those under 45 at migration showing some decline in risk.

The first Health and Nutrition Survey of the United States was conducted in 1971-74 by the National Center for Health Statistics. This survey assessed the nutritional status of 23,000 representative American adults. This population has been successfully followed-up for mortality and cancer incidence, and a number of analyses are currently underway to assess the relationship between nutritional variables and cancer risk. Among the first analyses are studies of calcium and vitamin D intake, a study of lung cancer focusing on carotene and fruit and vegetable intake, an evaluation of a variety of nutritional and other risk factors for prostatic cancer, an assessment of cancer risk associated with artificial sweetener use, and an evaluation of cancer risks associated with coffee, caffeine, and methylxanthine consumption.

A case-control study of colorectal cancer is focusing on fecal mutagen level as a possible risk factor for this disease. Fecal mutagenicity and fecapentaene, a newly-identified, potent fecal mutagen, will be measured in all subjects in the study. The effects of diet, medical workup, surgery, recovery, and disease status on fecal mutagen level will be determined. It is anticipated that this methodologically-oriented study will provide a sound basis for future interdisciplinary assessments of dietary and other risk factors for colon cancer.

A large-scale, population-based, interdisciplinary study of four tumor sites that are excessive in the black population (esophagus, pancreas, prostate, and multiple myeloma) is currently being designed. A major focus of this investigation will be to assess nutritional risk factors for these tumors, and to determine the extent to which these and other risk factors might explain the racial variation.

In collaboration with the Biostatistics Branch and the Division of Cancer Prevention and Control, as well as with the People's Republic of China, EEB investigators are participating in a variety of case-control studies in China to assess nutritional determinants of lung cancer, esophageal cancer, stomach cancer, and choriocarcinoma.

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

One of the larger examples of this type of investigation is the National Bladder Cancer Study. Recent findings from this study include: 1) A decrease in risk associated with the cessation of smoking or with switching from unfiltered to filtered cigarettes, after appropriate adjustment for the effects of duration of smoking. 2) A significant excess risk of 50 percent for males usually employed as truck drivers or delivery men. In addition, there was an increasing trend in risk with increasing duration of truck driving. These findings, coupled with experimental evidence of the mutagenicity and possible carcinogenicity of motor exhaust emission particulates, suggest a plausible role for motor exhaust exposure in human bladder carcinogenesis. Further analyses have also revealed excess risks for painters, railroad workers, metal machinists, metal workers, construction workers, lumbermen, and wood workers. 3) No excess risk was noted for tuberculosis chemotherapy, principally isoniazid. 4) Information from over 1,000 water utilities in the study areas was linked with the questionnaire data to evaluate water quality and bladder cancer risk. Overall, there was no elevation in risk for lifetime use of surface water sources compared to nonchlorinated ground sources. However, non-smokers showed excess risks for the use of chlorinated surface sources, with relative risks of 2.5 for those who used surface sources for at least 60 years.

Analyses of a separate bladder cancer study in high-risk areas of New England suggested a relationship to tobacco usage, truck driving, textile work, and leather work. The tobacco, truck driving, and textile findings revealed evidence of duration-response relationships. A case-control study of nasal cancer in rural areas of Virginia and North Carolina revealed an excess risk associated with work in the furniture industry for adenocarcinoma, and excess risks of squamous-cell tumors of two- to three-fold associated with cigarette smoking.

A large study of testicular cancer in young men focused on in utero and childhood exposures. These analyses revealed an elevated risk for undescended testis that increased with increasing age at correction of the condition. No increased risk was observed for the normally descended testis in men with unilateral maldescent, and only a slight risk was noted for men who had an inguinal hernia but not an undescended testis. Excess risks of testicular cancer were associated with a history of mumps orchitis and testicular trauma, but no excesses were noted for other childhood diseases, X-rays in childhood, venereal disease, or vasectomy. Analysis of interview data from mothers concerning events during pregnancy revealed a strong relationship between low birth weight and risk, and elevated risks for unusual bleeding during pregnancy, the use of a variety of CNS depressant drugs, and X-ray exposures. No excess risk was associated with the use of hormones during pregnancy. Analysis of over 300 cases and controls of intraocular melanoma revealed elevated risks associated with birth in the south, sun bathing, sun lamp use, failure to wear eye protection in the sun, and an increased number of freckles. These data suggest that sunlight exposure is an important risk factor for intraocular melanoma.

Analysis of over 600 cases of invasive cervical cancer and 1,000 controls from several U.S. centers revealed that the absence of regular pap smear screening was associated with a major elevation in risk, with those whose most recent pap smear was ten or more years prior to diagnosis being at a five- to six-fold excess risk compared with those screened more recently. Multiple sexual partners and early age-at-first intercourse were predictive of risk in this study. Particularly noteworthy were the associations of excess risk on the order of two-fold for both long-term (five years or greater) use of oral contraceptives and long-term cigarette smoking. An evaluation of cervical cancer in Panama likewise revealed excess risks for multiple sexual partners and long-term oral contraceptive use. Serologic study indicated that a large proportion of the subjects had antibodies to herpes simplex type II; however, there were no significant differences between the cases and controls.

Analyses were also conducted on case-control studies of mycosis fungoids, multiple myeloma, non-Hodgkin's lymphoma, and ovarian cancer. Intensive case-control evaluations currently in the field include an interdisciplinary study of colorectal cancer, studies of breast cancer and benign breast disease, and a study of choriocarcinoma.

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

A large number of interdisciplinary studies linking HTLV-I and hematopoietic malignancies are underway. A case-control study of these malignancies in Jamaica has indicated that approximately one-half of non-Hodgkin's lymphoma cases have antibodies to HTLV-I. In addition, molecular analysis has documented the presence of integrated viral DNA in all positive cases. The corresponding prevalence rates of antibody positivity in the general population is approximately five percent. In addition, 20 percent of B-cell chronic lymphatic leukemia cases were also HTLV-I antibody positive. Further laboratory studies have raised the possibility of a virally-induced T-cell immunologic purturbation predisposing to B-cell malignancy. Studies of HTLV-I infection in Jamaica have revealed an overall prevalence rate of five percent that increases with age among adults. A parallel study in Panama indicated a six percent prevalence rate, with no difference by age. In addition, a geographic gradient in prevalence of antibody positivity was noted in Panama ranging from one percent in the south to ten percent in the north. Further studies are underway in both of these countries to identify the characteristics of persons who are antibody-positive compared with those who are antibody-negative. More recently, we have identified Okinawa as a highly HTLV-I endemic area with rates of seropositivity in some age groups of the general population approaching 40 percent. High rates of antibody positivity were also noted in migrants from Okinawa to Hawaii and among their Hawaiian-born offspring. A number of family studies of HTLV-I infection are

underway to elucidate virus transmission and host-susceptibility factors. Among close family members of those with HTLV-I antibodies, the prevalence of antibody positivity is three or four times greater than that seen in the general population. In addition, to date, the mothers of all cases who have been tested have shown antibodies to HTLV-I. Finally, an immunosuppressive role for HTLV-I is suggested by the possible link in some cases to certain medical conditions, particularly clinical herpes zoster and parasitic infections.

The other major area of emphasis in this program area has been studies of HTLV-III, the etiologic agent for AIDS. In fact, the Branch was centrally involved in many of the studies linking HTLV-III to AIDS. These included an elucidation of the risk factors associated with both AIDS and antibodies to HTLV-III. Included were the risk factors of receptive anal intercourse with multiple partners in high-risk areas for homosexual men, a dose-related relationship to the use of commercial plasma products among hemophiliacs, and frequent needle injections among drug users. Seroepidemiologic studies of these high-risk cohorts have documented the progression from seroconversion to subclinical immunodeficiency to clinical manifestations, and have shown that full-blown AIDS develops in five to 20 percent of HTLV-III positive individuals in less than three years. Part of the methodologic developments required for these studies resulted in the extensive characterization of the sensitivity and specificity of a screening test for the identification of seropositive individuals. Monitoring of U.S. cancer registry data in AIDS high-risk areas documented a substantial increase in Kaposi's sarcoma and a lesser increase in Burkitt-like lymphomas. Finally, a number of investigations were begun in Africa, particularly Kenya and Zaire. Thus far, we have noted a surprisingly high prevalence of seropositivity for HTLV-I, HTLV-II, and HTLV-III among healthy subjects. There is marked regional variation in positivity that seems to correspond to malarial prevalence. Thus far, there is no evidence of either HTLV-III infection or immunosuppression underlying the occurrence of the endemic form of Kaposi's sarcoma which occurs excessively in portions of Africa. We are currently exploring the specificity of the observed reactions in antibody assays and other tests for retroviruses. Distinguishing the various forms of the natural history of HTLV-III infection, as well as its relationship to a number of clinical states, including a variety of malignancies, is the general thrust of a large number of studies currently in the field.

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

The interdisciplinary project of familial melanoma continued to demonstrate the effectiveness of this research strategy. In the past year, this project has led to: 1) the publication of a full-color atlas depicting the clinical spectrum of dysplastic nevi; 2) the quantification of risk of melanoma in these families, where the cumulative lifetime risk of melanoma approaches 100 percent in those family members with dysplastic nevi; 3) proof that dysplastic nevi are the formal precursors of the melanomas which occur in this setting; 4) demonstration that the melanoma and dysplastic nevus traits represent the pleiotropic effects of a single, highly penetrant, autosomal dominant gene; and 5) replications of the observation of a hypermutability state in response to UV light exposure among those with dysplastic nevi.

The previously described presence of a radio-resistant phenotype in the cells of patients with the Li-Fraumeni cancer family syndrome has been extended to several kindreds and then correlated with the expression of the oncogene c-myc in cells demonstrating this radio-resistance. An increased risk of testicular cancer was described among patients with polythelia, and a pattern of urogenital anomalies noted in members of families prone to testicular cancer.

A major new interdisciplinary study of the dominantly inherited nevoid basal cell carcinoma syndrome has been initiated, with the ultimate goal of including between 150 and 200 members of several multigeneration-affected families. This study will attempt to define the spectrum of associated malignancies in persons with this syndrome, to characterize the clinical features of the syndrome, to clarify the relationship between UV radiation exposure and malignant transformation in family members, to map the responsible gene through genetic-linkage analysis, and to develop a repository of biological specimens for use in collaborative studies to elucidate the molecular pathogenesis of this syndrome.

Finally, a repository of biologic specimens from high-risk family members continues to provide valuable materials for experimentalists investigating susceptibility mechanisms in carcinogenesis. After years of minimal interest by our laboratory colleagues, the development of a variety of new molecular probes and the identification of a number of different putative human oncogenes has led to considerable enthusiasm for access to the material from particular families.

Immunoepidemiology: The Branch is engaged in a number of studies to evaluate populations with altered immune function to clarify the relationship between immune function and malignancy. The risks of cancer of different sites are quantified for these various groups of patients, and the characteristics and determinants of unusual risk are sought. The populations under study include renal transplant recipients, patients with diseases which alter immune function (end-stage renal disease, sicca syndrome, gluten-sensitive enteropathy, sarcoidosis, scleroderma, Crohn's disease). While a number of studies are underway, little in terms of results have come from this program area within the past year. The most notable results are those just emerging

from analyses of a population-based survey of T-cell subsets and their determinants. Based on the obvious value of measuring T-cell subsets for use both as a surrogate measure of exposure, and as evidence of disease process, we determined that much more about the determinants of these subsets in the normal population needed to be understood, so that this tool could be most effectively used in a variety of epidemiologic investigations. As a result, a population-based survey in the Washington, D.C., metropolitan area was conducted in order to assess the determinants of the subset variations in the general population. Preliminary results have indicated that these subsets vary significantly by age, race, and sex, and that cigarette smoking results in significant alterations in the T-cell sub-populations of otherwise healthy persons.

Currently, follow-up investigations of a variety of acquired diseases that result in altered immunity are being conducted within the Veterans Administration hospital records system. In addition, follow-up has been completed for the 3,000 hyperimmunized former employees of a biologic warfare research center, and analyses are currently underway.

The implication from the wide variety of studies conducted in the past in this area is that in a general sense, impaired immunologic surveillance is probably not etiologically important for most human malignancy. Rather, particular immune disorders are related to specific patterns of malignancy. Linkage of the clinical immunologic aberrations in these diseases with the cancer risks may provide useful insights into the mechanisms of immune regulation of human carcinogenesis.

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

A case-control study of canine cryptorchism revealed a nine-fold risk of testicular neoplasia. A four-fold risk of testis cancer was noted for animals with inguinal hernia. In addition, in high-risk closely related breeds of dogs, the relative risk of cryptorchism was inversely associated with adult size, suggesting a role for physical size or the rate of growth for this congenital malformation. A survey of pet dogs seen at Michigan State University veterinary teaching hospital, 1978-1981, found those diagnosed with hepatic and other neoplasms, associated with polybrominated biphenyls (PBB) in laboratory experiments, were considerably younger than corresponding animals diagnosed with similar neoplasms between 1969-1972, the period immediately preceding the environmental accident of PBB food contamination in Michigan. Further data are being sought in an analytic investigation to determine whether these descriptive findings indicate that PBB may be acting as a tumor promotor in the field, as it seems in the laboratory.

Recent acquisition of the service records and a complete computerized file of standard post-mortem data on the military working dog population has permitted the initiation of a systematic linkage of disease to prior medical history, "occupational" exposures, diet, and other factors among 7,000 military working dogs.

General Environment: The impact on cancer risk of general environmental exposures (air and water pollution) is perhaps the most difficult of all to assess. Difficulties include: (a) a lack of specificity of hypotheses; (b) exposures that are difficult to measure, particularly for the time period of relevance of cancer induction; and (c) average doses which could be expected to produce low-level elevations in relative risk. Historically, we have done little as a Branch in this general area. Recently, we have ventured into some of these assessments by attempting to take advantage of improvements in methodological approaches. A variety of laboratory studies have raised suspicions about a number of chemical carcinogens in drinking water. Correlational studies of cancer mortality rates and direct or surrogate measures of these chemicals show varying results, with a few relatively consistent findings, among them a positive association with urinary bladder cancer. As a result, an aggressive attempt was made to test this hypothesis in the National Bladder Cancer Study. Specifically, persons were interviewed for their lifetime residence histories, which included questions about the source of their drinking water at these various locations. In parallel, the Environmental Protection Agency surveyed the purveyors of water in these areas for their past practices as to the source of the water and its chemical treatment. In addition, chemical measurements in current water supplies were taken and related to characteristics of the source of the water and its chemical treatment. Analysis has failed to yield consistent evidence of increased risk with exposure to water likely to be relatively high in trihalomethanes or related chemicals. There did appear to be notable interaction of duration of such potential exposure with cigarette smoking. Among non-smokers the relative risk of bladder cancer was directly related to duration of exposure, while among smokers a negative trend was noted. In addition, regional differences in the analysis have raised the question of increased risk related to other contamination of water supplies, such as chemicals used in agriculture. These same general methods of exposure assessment have been applied to field studies of other cancer sites that were initiated for different reasons.

Our attempts at evaluating air pollution have been fewer. Because of the known relationship between arsenic exposure and lung cancer risk in the occupational setting, the substantial amount of arsenic placed in the atmosphere by non-ferrous metal smelters, and the generally elevated rates of lung cancer in both sexes in counties containing such smelters, the Branch completed a study which attempted to assess the influence of general arsenical pollution. In this investigation, the risk of lung cancer was directly related to two measures of potential general environmental exposures among non-occupationally-exposed persons (proximity to the smelter and arsenic in the soil). This study has increased the confidence of epidemiologists in testing at least some concerns about general atmospheric pollution. The

proposed study of lung cancer in Shanghai, China, is also being undertaken because general environmental exposures may contribute to the elevated rates in Chinese women, among whom cigarette smoking is not prominent.

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

Potential epidemiologic resources within 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.

This is a program area to which all of the Sections within the Branch contribute. Because of this, a complete description of these activities for the Analytical Studies Section is reviewed in the summary report of the Biostatistics Branch to which this Section was transferred during this year. In addition, research in methods of survey research continued and included assessments of random digit dialing as a means of choosing population-based controls, and the use of computer-assisted telephone interviewing to enhance the speed and accuracy of telephone-based interviews. Issues involved in the assessment of dietary intake were also evaluated. One study demonstrated that total vitamin A intake is well predicted by intake of a few selected dietary items, while another critiqued the calculation of odds ratios using a surrogate measure of intake.

Various aspects of analysis of epidemiologic data were also explored. This included continued development of SAS pre-program subroutines to estimate and test relative risks and to facilitate conditional regression modeling with matched case-control data. Further refinements of case-control methods for estimating population attributable risks associated with multiple risk factors were also explored.

Reviews: A major role of the Branch is to provide comprehensive and critical reviews of etiologic factors in cancer. These reviews take the form of chapters in books, review articles for journals, or, occasionally, reports for various legislative or regulatory bodies. This year, comprehensive reviews have been written summarizing a variety of aspects of the relationship between retroviruses and diseases, including hematopoietic malignancies and AIDS. A number of reviews have also been written about various aspects of familial melanoma and the dysplastic nevus syndrome, as well as about the value of the familial study approach to identification of etiologic factors. The epidemiology of specific cancer sites are often the subjects of such reviews, including multiple myeloma, testicular cancer, ovarian cancer, and cervical cancer during this year. General reviews of the relationship between occupational factors and malignancy have been prepared, while others have

focused on important specific topics in the area of occupational cancer, including formaldehyde, silica and other non-organic dusts, and brain tumors related to occupational exposure. The prospects and problems associated with the rapidly emergent area of biochemical epidemiology was the basis of one interdisciplinary review. Finally, a summary of the methods and applications of epidemiology into etiologic research on cancer was provided for the document on the scientific basis for regulation of carcinogens recently published by the Office of Science and Technology Policy of the White House. The Branch views these reviews not only as up-to-date summaries of topical issues in cancer etiology, but as an opportunity to critically review and plan our own opportunities in a number of these various areas.

OTHER ACTIVITIES:

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

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

Although the Branch encourages an atmosphere of academic freedom and the development of new ideas and approaches, these innovations undergo critical review and evaluation through several mechanisms. These include frequent section and branch meetings; close contacts with support service and collaborating groups; various formal review mechanisms by internal and external committees; several working groups (e.g., data resources, female tumors, family studies, and drug studies); interagency committees; the Clinical Center Review Committee involving clinical investigations; careful scrutiny of questionnaires and protocols prior to and during clearance through governmental channels; ad hoc external review groups for major studies (e.g.,

National Bladder Cancer Project, formaldehyde study); the NIH Coordinating Epidemiology Committee; and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors of 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 (8 contracts) were initiated to clarify the role of various environmental and host determinants of the etiology of malignant neoplasms. Specifically examined are associations of cancer and nutritional factors, drugs, other lifestyle factors, and prior disease. The areas covered by these contracts include 1) studies examining breast cancer in Oriental Americans, 2) studies on environmental cancer using prepaid health plans, 3) a follow-up study of women evaluated for infertility, and 4) investigations of cervical cancer in Latin America.

Studies Examining Breast Cancer in Oriental American Women (3 Contracts):

There is some reason to believe that, if a substantial amount of the international variation in breast cancer is due to dietary differences, the relevant age is likely to be the pre-pubertal period and perhaps adolescence. These ages have also been considered a critical time for breast cancer induction from entirely different lines of evidence (e.g., the interactions of other breast cancer risk factors with age and from experimental studies). A recent Breast Cancer Task Force workshop on diet and breast cancer concluded that dietary investigations of breast cancer needed to be shifted towards evaluation of dietary differences at younger ages, particularly in view of the lack of any major positive findings from recent studies relating adult diet to risk of breast cancer.

Oriental Americans constitute a group in which diet in the home at young ages can be assessed by the case-control method. Cases and controls and their mothers will be interviewed in order to assess lifetime dietary patterns. The most important analytic variable will be one which can be assessed reasonably well in a case-control interview context, that is, "traditional" diet versus more westernized diet. It is hoped to evaluate differences in risk between a primarily traditional diet in the home throughout life, a primarily westernized diet throughout life, and a relatively traditional diet within the home at young ages but a westernized diet later. It is also planned to quantify the difference in rates between Oriental Americans and Caucasians in relation to recognized breast cancer risk factors (including age at menarche), and the difference explained more directly by diet or other factors.

The study design involves identification of newly incident cases of breast cancer among young Oriental Americans (less than age 55) and interviews of these women and a comparable matched control series of Oriental Americans to obtain standard breast cancer risk factors and some information about diet (particularly major dietary changes over life). At the time of interview, the name, location and phone number of the subjects' mothers will be obtained. Telephone interviews with mothers will be carried out to assess general dietary practices in the home when the study subject was growing up.

The Cancer Center of Hawaii, Northern California Cancer Program, and University of Southern California possess population-based registries which have been in existence for at least two years and which cover an Oriental-American population large enough to yield at least 100 breast cancers among Oriental Americans less than 55 over a 5-year period. Epidemiologists from these areas have collaborated with the NCI Project Officer to develop a protocol and questionniare for the study. Following this phase, each area will collect the information designated in the protocol. The analyses and interpretation of the results will be a collaborative effort between NCI investigators and these epidemiologists.

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

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

In the Southern California contract, the surgical record books from the Southern California Permanente Medical Group from 1952 through 1970 have been reviewed manually to identify a group of health plan members who had oophorectomy during this time period. These lists were compared with a list of breast cancer patients identified by the health plan's tumor registry during the years 1972-1977 in order to identify patients with a history of oophorectomy who subsequently developed breast cancer. From the same surgical record books and the files of health plan members, four controls for each case were drawn. These controls are women having undergone an oophorectomy in the same year as the case, matched on age at which this operation occurred, and duration of health plan membership (to the date of diagnosis of the case). Breast cancer risk factors and hormonal replacement therapy information are being abstracted from these patients' charts. An additional study of estrogens and other risk factors as they relate both to breast cancers and abnormal mammographic findings is also being conducted. The potential teratogenicity of estrogens is also being evaluated via a case-control evaluation of drug exposures during pregnancy and subsequent development of limb-reduction and cardiac defects in the fetus.

The investigators in Southern California will analyze their own data and in addition will send a copy of the material to NCI so that the data can be merged with similar information obtained from the two other Kaiser Permanente Health Plans. New evaluations in the project will include assessment of drugs in relationship to endometrial carcinoma and further evaluation of potential teratogenicity of various medications.

In Northern California data collection was completed for a case-control study of ovarian cancers similar to that in Portland. Using a protocol for a case-control study of patients who developed breast cancer after having

had a bilateral oophorectomy, data collection was undertaken and is nearing completion. The major exposure of interest being assessed in this study, in addition to the usual breast cancer indicators, is the use of menopausal estrogen replacement therapy. Both the Northern California and the Portland Plans have submitted information on malignancies occurring in the health plans and various other demographic information concerning potential hypotheses to be explored in these health plans. There have been extensive evaluations of cancer incidence among various industrial groups covered by the prepaid plan, and a number of analytic studies based on these evaluations are currently being designed. Two new evaluations were begun: a study of the relationship of serum cholesterol levels among men attending a multiphasic screening exam and their subsequent risk of malignancy and a case-control study of patients with leukemia and lymphoma which will evaluate the risk associated with diagnostic irradiation.

In Portland, time trend analyses of cancer incidence in this plan are currently underway. The data collection phase of a case-control study of ovarian cancer has been worked out between the Portland region and the Northern California region under the direction of the NCI Project Officer. The focus of the study is on therapeutic drugs and medical conditions which alter the pituitary-ovarian hormonal axis. Data on stage of disease and survival of cholesterol level and risk of colon and lung cancer in men, and diagnostic irradiation and the risk of leukemia and lymphoma, are in the data-collection phase.

New, planned studies in Portland and in Northern California include evaluations of the interrelationships between oral contraceptive use and benign and malignant breast disease, drug use and reproductive factors for endometrial cancer, and follow-up studies based on findings from the cholesterol, occupational, and radiation studies currently being conducted or analyzed.

A Follow-up Study of Women Evaluated for Infertility (1 Contract):

Nulliparous women and women with a late first pregnancy are at an increased risk of developing certain neoplasms, including those of the breast, endometrium, and ovary. The reasons for this excess risk are not known. Among the possible reasons suggested have been either a change in the hormonal milieu consequent to first pregnancy or abnormal profiles associated with absolute or relative infertility. Studying a cohort of women treated for infertility will allow comparison of disease incidence among subgroups with differing abnormalities and may aid in understanding the mechanisms of carcinogenesis. If an abnormal hormonal milieu is the important factor contributing to an excess cancer risk among infertile women, those women with specific identifiable hormonal problems will be of particular interest. The follow-up study of women with recognized problems of infertility will allow evaluation of a hypothesis regarding breast cancer etiology that has received recent widespread attention. This hypothesis proposes that women who exhibit luteal phase defects may be at increased risk due to their relatively unopposed state of endogenous estrogens. The

present study will not only allow evaluation of effects of varying hormonal states, but will allow examination of various infertility treatment effects. Of particular interest will be radiation exposures to the pituitary and/or ovaries and use of progestational agents.

The methodology is a retrospective cohort study. Approximately 3,000 women evaluated for infertility during a 30-year period (1935-1955) have been followed to the present time for subsequent disease risk. Medical records have been abstracted to obtain the following information: demographic characteristics, menstrual and reproductive history, the diagnostic work-up for infertility, and infertility treatment details. Follow-up information on subsequent reproductive events, development of malignancies and vital status (including cause of death) was sought through personal contact and through a population-based tumor registry. Data are currently being analyzed using standard methods for prospective studies that employ internal comparisons (e.g., comparing events rates for those with and without a progesterone deficiency) and external comparisons.

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 also, possibly, smoking and oral contraceptive use. The findings regarding sexual behavior suggest that cervical cancer may be caused by a virus (or other microorganisms) transmitted during sexual intercourse. Much attention has focused on the possible role of herpes-simplex virus type 2, as well as more recently on papillomavirus, although neither agent has been implicated with any 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 recent 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 thus proposes to: 1) identify characteristics of Latin American women that are predictive of risk of developing invasive cervical cancer; 2) identify behavioral characteristics of Latin males that may contribute to the high disease rates; and 3) relate certain biochemical measurements, in both males and females, to risk. Included for study will be approximately 800 women with invasive cervical cancer from four Latin American countries (Colombia, Costa Rica, Mexico, and Panama) and 1600 matched controls. Personal interviews will be conducted with these women, and blood and cervical scraping material obtained. In addition, the study will include male subjects, who will comprise the husbands of the sexually monogamous women. These male study subjects will be interviewed in conjunction with a physical examination that will focus on hygiene, circumcision status and evidence of infection. Blood samples will also be obtained.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 85

ENVIRONMENTAL STUDIES SECTION

Institution/Principal Investigator/ Contract Number	Title
Cancer Center of Hawaii Abraham Nomura NO1 CP 21036	Breast Cancer in Oriental 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
Mayo Foundation George D. Malkasian NO1 CP 11023	Follow-up Study of Women Evaluated for Infertility
Northern California Cancer Program Donald Austin NO1 CP 21010	Breast Cancer in Oriental Americans
Southern California, University of Brian Henderson NO1 CP 21038	Breast Cancer in Oriental Americans
Gorgas Memorial Institute William C. Reeves	Investigations of Cervical Cancer in Latin America

SUMMARY REPORT

POPULATION STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The Population Studies Section has responsibility for the acquisition and utilization of resources to facilitate epidemiologic studies. These studies range from descriptive to analytic, including case-control and cohort studies. Liaison is maintained with government and non-government sources to realize these objectives. That which follows are summaries of several activities within the Section which are supported by research contracts (2 contracts - $980,000.00).

Assessment of Screening: Data have been abstracted on all persons ever screened for bladder cancer (1581), as well as all persons known to have developed bladder cancer among the Chambers Works employees (316) regardless of whether they had been screened. Complete work histories were abstracted, which included dates of employment by job title for the duration of employment by DuPont. Medical histories have been abstracted for both cases and non-cases, which include the dates and results of every urinary cytologic reading, the dates and results of every urinary blood test, and the dates and type of every physical exam which the persons had been given, as well as vital status information. For each bladder cancer case detailed clinical histories were abstracted to provide information concerning signs or symptoms of bladder cancer, procedures performed, findings of these procedures, and any recommendations made. Detailed pathologic information has also been abstracted to include type, grade, stage, evidence of multicentricity, metastatic sites, and also any second primary sites of malignancy. A 2-fold difference between cases and non-cases was detected for hematuria, and level of severity of cytology was significantly greater among cases than non-cases (6-fold) controlling for level of exposure. Among cases an increasing trend for level of severity of cytology was detected with increasing levels of exposure. Ongoing analyses are pursuing the identification of clinical signs and symptoms which occur prior to the date of diagnosis of the first malignant tumor of the bladder as they relate to exposure.

Lung Cancer in New Jersey: A case-control study of incident lung cancer among male residents of previously identified high-rate areas of New Jersey is presently being analyzed. Emphasis has been given to smoking, occupation and diet. Interviews were successfully completed on 763 cases and 900 controls. Comparable odds ratios for cigarette smoking were found for each of the three major cell types: squamous, small cell and adenocarcinoma. An examination of the effect of smoking cessation found 5-fold risks after 25 years since the person last smoked. All analyses were adjusted for age, study area, respondent type, pipe and/or cigar smoking, consumption of dark green vegetables, reported exposure to asbestos, employment in shipbuilding and employment in other high-risk jobs. Occupational analyses have found shipbuilding workers, plasterers and lathers and boilermakers to have significantly elevated risks. Masons and tilesetters, janitors and

cleaners, printing workers and trucking service, warehousing and storage workers were found to have excess risks associated with duration of employment. In order to assess whether dietary intake of carotene, preformed retinol, or total vitamin A modified the risk of lung cancer, subjects were asked about their usual frequency of consumption, several years earlier, of 44 food items which provide 83% of the vitamin A in the American diet. The men in the lowest quartile of carotene intake had 1.3 times the risk of those in the highest quartile after adjustment for smoking intensity and duration and education. No association was seen for retinol or total vitamin A.

A statewide study of incident lung cancer among females completed its data collection phase in late 1984. Data editing is being completed at this time. Analyses of these data will pursue the roles of smoking, occupation and diet as well as hormonal factors as they relate to the risk for lung cancer by cell type among women.

Lung Cancer in Louisiana: Smoking was shown to be a strong determinant of the high lung cancer rates seen in the southern Louisiana area, with the use of hand-rolled cigarettes associated with especially high risk. Low fruit intake, another risk factor noted, was especially prevalent among those persons calling themselves "Cajuns". Exposure to wood dust either occupationally or at home led to elevated risk estimates.

The occupational analysis for males in the Louisiana lung cancer study revealed increased risks among non and light smokers for several industrial categories including lumber manufacturing, construction, and fishing while showing no increase in risk among the moderate and heavy smokers. Significantly elevated risks for exposure to wood dust and mineral oil mists were also restricted to the non and the light smokers. Other consistent findings included elevated risks for persons living near a lumber manufacturing site and for those exposed to wood dust in their leisure activities. The high levels of smoking in Louisiana and the types of tobacco used may be masking the risk due to occupational exposures in all but the non and the light smokers.

Passive Smoking: Smoking data for the spouses of nonsmoking participants in the Louisiana and New Jersey lung cancer studies revealed a dose dependent excess risk of lung cancer with increasing levels of passive smoking exposure among nonsmoking persons married to a smoking spouse. This effect was seen primarily among females who were much more likely to be nonsmokers and have spouses who were heavy smokers. The excess risk appeared to be restricted to squamous and small cell carcinomas of the lung.

Lung Cancer in Selected Texas Counties: Analyses of data from this population-based case-control study of incident lung cancer have focused on smoking, occupation and diet. Among white females the three major cell types were related to cigarette smoking (small cell, squamous, and then adenocarcinoma from highest to lowest risks). Over 90% of the female cases had smoked at some time. Excess risks among white males were found for those

men who had worked in the construction, chemical, metals, or transportation industries. Dietary analyses have detected a slight protective effect of vegetable intake for both adenocarcinoma and squamous cell carcinoma.

Laryngeal Cancer in Selected Texas Counties: A population-based case-control interview study of incident laryngeal cancer has been analyzed in an attempt to identify occupational risk factors for this disease. Our analysis included 183 white Texas men with squamous cell carcinoma of the larynx and 250 frequency matched controls. Occupational risk factors for laryngeal cancer were examined controlling for potential confounding by cigarette smoking, alcohol consumption, and fruit and vegetable consumption. Industrial and occupational categories based on the major groups in the Standard Industrial Classification System and the Dictionary of Occupational Titles were formed, as were groupings of potential high risk job titles. Significantly elevated risks were seen for study subjects employed in the transportation industry, as metal fabricators, and in construction. Excess risks were also seen for men employed as maintenance workers or wood workers. Elevated risks were not found for shipbuilding or petroleum/chemical manufacturing, two previously hypothesized high risk industries.

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

Population Estimates: The Bureau of the Census is developing estimates of the resident population of the U.S. at the county level by age, race and sex for the 1980s. During FY85 the Bureau will provide annual estimates through 1984. Models have been developed which utilize special censuses, decennial censuses, and medicare registration to provide these estimates. Prior estimates for the 1970s have been revised using the 1980 census. Special emphasis has been given to the development of estimates for the black population at the county level. The Bureau of the Census continues to respond to requests for special population estimates.

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

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

CONTRACTS ACTIVE DURING FY85

POPULATION STUDIES SECTION

Institution/Principal Investigator Contract Number	Title
Bureau of the Census Richard Irwin Y01 CP 20517	Population Estimates by Age, Race, and Sex for the 1980's
Capital Systems Group, Inc. Kent Boyd N01 CP 31024	Biomedical Computing - Design and Implementation

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04378-10 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

U.S. Cancer Mortality Survey

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

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

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

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Population Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The overall objective of this project is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigations to test specific etiologic hypotheses. This project will continue at this reduced level of personnel commitment which should prove adequate to periodically update our earlier publications.

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

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

Major Findings:

The major activity on this project this fiscal year has been an attempt to identify places (State Economic Areas) within the U.S. which are experiencing differential rates of change of site-specific cancer mortality relative to the country as a whole. Logistic modeling has identified places which are experiencing greater rates of increase and also smaller rates of decline than comparable national rates. These places are likely candidates for more in-depth analytic studies which will focus on etiologic determinants. Anatomic sites of specific interest are the lung, colon, and rectum.

Significance to Biomedical Research and the Program of the Institute:

This project provides a continually expanding data set which has generated specific etiologic hypotheses concerning cancer. The capability of subdividing the data set into specific racial and geographic subsets (e.g., county level analyses) also provides an opportunity to test specific etiologic hypotheses.

Proposed Course:

The project will continue to pursue etiologic questions and will periodically update our earlier publications. The personnel commitment to this project has diminished to a maintenance level which would appear to be adequate for the next several years.

Publications:

Pickle, L.W., Mason, T.J., Howard, N., R., Fraumeni, J.F., Jr.: Atlas of Cancer Mortality Rates and Trends Among Whites: 1950-1980. Washington, D.C., U.S. Government Printing Office, 1985, 311 pp.

CONTRACTS IN SUPPORT OF THIS PROJECT

BUREAU OF THE CENSUS (YO1-CE-20517)

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

Current Annual Level: $10,000.00

Man Years: 1.0

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

Major Contributions: This support contrac4 is critical to the continuation of this project, for it provides estimates of populations at risk for cancer at the county level.

Proposed Course: This interagency agreement will continue until this resource is no longer needed.

CAPITAL SYSTEMS GROUP, INC. (NO1-CP-31024)

Title: Biomedical Computing - Design and Implementation

Current Annual Level: $970,000.00

Man Years: 28.0

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

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

Proposed Course: This contract will support this activity as needed. To date this project has utilized approximately 1.0 man years, of this Contractor's time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04410-09 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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.H. Greene	Deputy Branch Chief	EEB	NCI
Others:	W.A. Blattner	Chief, FSS	EEB	NCI
	M.A. Tucker	Clinical Investigator	EEB	NCI
	D.L. Mann	Senior Investigator	LHC	NCI
	D.J. Tollerud	Research Associate	EEB	NCI
	S.J. Bale	Staff Fellow	EEB	NCI
	R.C. Young	Chief, MB	MB	NCI
	J.J. Mulvihill	Chief, CGS	CEB	NCI

COOPERATING UNITS *(if any)*

Dept. of Surgery, USUHS (D.M. Strong); Biotech Laboratories (A. Bodner); Flow Laboratories (L. Blackwood); Westat, Inc., (J. Cahill); ORI (D. Switalski)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.5	6.2	1.3

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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

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

PROJECT DESCRIPTION

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

M.H. Greene	Deputy Chief	EEB	NCI
W.A. Blattner	Chief, Family Studies Section	EEB	NCI
M.A. Tucker	Clinical Investigator	EEB	NCI
D.L. Mann	Senior Investigator	LHC	NCI
D.J. Tollerud	Research Associate	EEB	NCI
S.J. Bale	Staff Fellow	EEB	NCI
J.F. Fraumeni Jr.	Associate Director	E&B	NCI
R.N. Hoover	Chief	EEB	NCI
J.D. Boice Jr.	Chief	REB	NCI
J.J. Goedert	Cancer Expert	EEB	NCI
J.W. Clark	Research Associate	EEB	NCI
N. Caporaso	Research Associate	EEB	NCI
E. Harris	EIS Officer	EEB	NCI
M.C. Fraser	Nurse Epidemiologist	EEB	NCI

Objectives:

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

Methods Employed:

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

studies of the late effects of cytotoxic drugs, standard cohort and case-control methods are used.

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

Family Studies Resources:

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

Malignant Melanoma:

This project is now in its ninth year, employing the interdisciplinary research strategy outlined above. Accomplishments during the current year include: (a) the publication of a full-color atlas depicting the clinical spectrum of dysplastic nevi; (b) quantification of the risk of melanoma in members of melanoma-prone families: the cumulative lifetime risk of melanoma approaches 100% in family members with dysplastic nevi; (c) demonstration that prospective monitoring of high-risk family members leads to the diagnosis of a substantial number of surgically-curable melanomas; (d) proof that dysplastic nevi are the formal precursors of the melanomas which arise in this setting; (e) demonstration that the melanoma and dysplastic nevus traits represent the pleiotropic effects of a single, highly penetrant, autosomal dominant gene; (f) definitive rejection of the hypothesis that a melanoma susceptibility gene is linked to the human major histocompatibility complex; and (g) development of a conceptual model of human tumor progression utilizing the neoplasms of the melanocytic system as its basis.

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

Laboratory work on the hereditary melanoma data base continues to provide new information. The presence of a hypermutability state in response to UV light exposure has been extended to include a larger number of study subjects, all of whom show an elevated mutation rate. Attempts to apply restriction fragment length polymorphism technology to the hypothesis that the melanoma/DNS gene is linked to the Rh blood group gene on the short arm of chromosome 1 has been hampered by difficulties in identifying polymorphic DNA probes for the genomic region near Rh. The only useful probe identified thus far is beta-nerve growth factor, which yielded a strong negative lod score (not surprising as it is not located near enough to Rh to have expected a positive result). This technique was used to exclude linkage to the Ha-ras oncogene on chromosome 11p, a hypothesis which surfaced elsewhere in the literature during the past year. DNA repair studies revealed a striking increase in G2 radiosensitivity in several high-risk families, an abnormali that correlated closely with clinical status of family members. Chromosome studies have revealed a significant excess of random chromosome structural and numerical abnormalities in family members with melanoma and/or DNS compared with unaffected family members and spouses. This observation suggests the hypothesis that chromosomal instability or fragility may contribute to melanoma susceptibility in these families.

Analysis of a case-control study of intraocular melanoma has demonstrated a pattern of differences between cases and controls which provides the first solid evidence that this tumor is related to sunlight exposure. Persons born in the southern United States were at 3.1 times greater risk of intraocular melanoma than persons born in more northern latitudes. Regular use of hats, visors and sunglasses protected against this cancer. Current analyses of this data base are concentrating upon the role of occupational and medication (particularly hormonal) risk factors. A report was published describing an 8-fold excess of melanoma in a large cohort of patients with Hodgkin's disease, an excess that in part was attributable to the malignant transformation of dysplastic nevi.

Lymphoproliferative and Hematopoietic Cancers:

Study of a family prone to hairy cell leukemia continues, with the current focus on HLA factors at the DNA level. HLA-DR genomic probes are being employed to

determine whether the DR blank found in affected family members is a consequence of a gene deletion. A survey of HLA phenotype distribution in 120 patients with cutaneous T-cell lymphoma has now been completed and is under analysis. Preliminary results indicate significant differences between cases and controls at the HLA-DR locus. A case-control study of cutaneous T-cell lymphoma is being analyzed in collaboration with the Environmental Studies Section. A similar collaboration has resulted in a report of an excess risk of multiple myeloma in North Carolina furniture workers, particularly those born before 1905 and those dying before age 65.

The population-based survey of T-cell subsets and their determinants has completed data collection and is now in analysis. Preliminary results indicate that T-cell subsets vary significantly by age, race and sex, and that cigarette smoking results in significant alterations in the T-cell subpopulations of otherwise healthy persons. A genetic polymorphism in the expression of the T4 (helper/inducer) receptor has again been identified in non-white study participants. This anomaly is inherited in an autosomal codominant fashion, and is not observed in Caucasian individuals who do not have black or native American ancestry.

Sarcomas:

The presence of the radiation-resistance phenotype in the cells of patients with the Li-Fraumeni syndrome has been extended to several kindreds. The current emphasis has been on correlating the presence of this phenotype with oncogene expression in the same cells. Preliminary results indicate that expression of the oncogene c-myc is increased in cells which demonstrate the radioresistance phenotype.

Genitourinary Cancer:

Complex segregation analysis of 16 families prone to ovarian cancer is now underway. A new family prone to testicular cancer was evaluated, seeking evidence of polythelia and dysmorphic features as possible risk factors. Minor dysmorphic features were found, but no polythelia was observed. Publications describing urogenital anomalies in members of families prone to testicular cancer, and the increased risk of testicular cancer in association with polythelia (both described in last year's report) have now appeared in print. A testicular cancer cluster has been identified in Pennsylvania which is currently being investigated. A protocol has been submitted to and approved by the Centers for Disease Control, under which members of our section will undertake a formal genetic analysis of data collected on family history of cancer among a population-based series of probands with cancers of the ovary, endometrium or breast. This study will represent the largest unbiassed series of cases available for such analysis, which will be done using state-of-the-art techniques of segregation analysis (see Genetic Methods, below).

Gastrointestinal Cancer:

Oncogene studies are currently underway on tissues derived from members of families at high risk of colon cancer. No results are yet available. HLA

typing of 26 members of 3 Alaskan families prone to hepatocellular carcinoma has been completed; no evidence of linkage between disease susceptibility and HLA was identified. Plans are now being made to conduct a formal comparison of family history of cancer as obtained from standard epidemiologic questionnaire and from detailed investigation of medical and vital records. The latter is the presumed "gold standard" against which the accuracy of reported family history will be measured. This study will use data collected in the study of colorectal cancer in rural Nebraska.

Nevoid Basal Cell Carcinoma Syndrome:

Project staff have initiated a major new interdisciplinary study of the autosomal dominant condition known as the nevoid basal cell carcinoma syndrome (NBCCS). We plan to evaluate and obtain biological specimens from 150 to 200 members of 7 multigeneration families, with the following goals: (a) to define the spectrum of associated cancers in persons with NBCCS; (b) to characterize the clinical features of the syndrome and investigate the overlap between NBCCS and other cancer-prone syndromes; (c) to clarify the relationship between UV radiation exposure and malignant transformation by studying the in vivo effects of UV light and the in vitro effects of UV radiation and UV-mimetic chemical carcinogens; (d) to map the NBCCS gene by genetic linkage analysis; and (e) to develop a repository of lymphocytes and tumor tissue from well-characterized family members for use in collaborative studies to elucidate the molecular pathogenesis of the syndrome. This project is now well underway; 70 family members have been evaluated to date. Very early results from the linkage analysis have yielded suggestive evidence of linkage between the NBCCS gene and the amylase gene on chromosome 1p (lod = 1.2 at θ = 0.00). This finding is particularly provocative as this area of the genome was postulated a priori as a possible location for the disease gene. This study is being conducted in collaboration with the Clinical Epidemiology Branch and the Dermatology Branch of NCI, the Radiology Department of the Clinical Center, the National Institute of Dental Research, the National Eye Institute and the National Institute of Neurological and Communicative Disorders and Stroke.

Biochemical Epidemiology of Lung Cancer:

As one of the initial EEB efforts in applying sophisticated laboratory probes to an epidemiologically designed study, a case-control study of lung cancer is planned in collaboration with the Laboratory of Human Carcinogenesis. The current plan calls for 100 newly-diagnosed lung cancer cases and 200 controls. Half of the latter will be comprised of patients with chronic lung disease (deliberately chosen to obtain a group of heavy cigarette smokers), while the other half will include patients with newly-diagnosed colon cancer. All study subjects will be interviewed and donate a variety of biological specimens. One major hypothesis to be tested is that poor metabolizers of the drug debrisoquine are under-represented among lung cancer cases, as reported by British investigators. The other major component of the survey will assess the feasibility and utility of a variety of biochemical probes as markers of either disease susceptibility of exposure to relevant carcinogens. Urine samples will

be tested for carcinogen-DNA adducts on white cell DNA, carcinogen-membrane adducts on red cells, and cotinine. This study is still in the planning phase.

Genetic Methods:

Work continues on adapting the segregation analysis program POINTER for use on the NIH computer system. This effort is largely complete, and this powerful new program is now being tested using data collected in our study of familial Hodgkin's disease. This program will soon be applied to the data collected by the CDC's Contraceptive and Steroid Hormone Study (CASH) of women with ovarian, endometrial or breast cancer. A report outlining the statistical approach for detecting excess disease risk in families has been submitted, in collaboration with the Biostatistics Branch. Life-table methods for testing genetic models in diseases with variable and late age-at-onset have been applied to the hereditary melanoma data base, and produced important new support for the hypothesis that familial melanoma/DNS is caused by an autosomal dominant gene. Pitfalls inherent in the inappropriate application of linkage analysis have been described in a report dealing with HLA and hereditary melanoma. Problems created by inappropriate parameter selection, misclassification of study subjects and selective reporting of positive results were considered.

Comprehensive Reviews:

Project staff have published reviews of the epidemiology of multiple myeloma, ocular melanoma, testicular cancer, and the dysplastic nevus syndrome, the genetics of melanoma, laboratory studies in hereditary melanoma, and the utilization of high-risk families as a resource for etiologic studies.

PROJECT 2: THE CARCINOGENICITY OF CYTOTOXIC DRUGS

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

The use of cytotoxic drugs in the management of various diseases represents a very special circumstance in which humans are deliberately exposed to potentially toxic chemicals, many of which are known to be carcinogenic in laboratory animals. It is reasonable to use such therapy in patients with advanced malignant disease, most of whom would die without treatment. However, these drugs are now being used with increasing frequency in cancer patients with a much more favorable prognosis (in whom long-term survival can be anticipated) and in the management of various non-neoplastic conditions. Therefore, the need has arisen to clarify the late carcinogenic risks associated with the use of these compounds. Further, such studies provide a unique opportunity to explore

mechanisms of carcinogenesis in human subjects. Accordingly, EEB and REB have designed a series of studies to address these issues. Among the strategies employed are: (1) cohort studies--follow-up of patients with a particular index disease, with ascertainment of subsequent cancers and correlation of treatment for the index disorder with the risk of specific malignancies; (2) randomized cohort studies--similar to (1) except that patients studied are participants in randomized therapeutic trials; and (3) case-control studies--patients with a specific index disease and a specific subsequent cancer are compared with persons having the same index disease who have not developed a subsequent cancer to assess the role of therapy as a cancer risk factor.

Ovarian Cancer:

A study of 3363 one-year survivors of ovarian cancer is now in analysis. Preliminary results confirm that the excess risk of acute nonlymphocytic leukemia (ANL) and preleukemia (PL) is confined to chemotherapy-exposed patients. Radiation therapy appears to confer no additional risk of ANL/PL beyond that associated with alkylating agent treatment. Women treated with either single agent melphalan or single agent cyclophosphamide were analyzed in detail. Both agents were associated with a significantly increased risk of ANL/PL, and evidence for a positive relationship between drug dose and leukemia risk was also found for each agent. In particular, a strong, statistically significant trend of rising risk with increasing dose was found for melphalan. Melphalan was 3.6 times more likely to cause ANL or PL than was cyclophosphamide, suggesting that in situations where each is therapeutically effective (as is the case in ovarian cancer), cyclophosphamide represents a safer treatment option. No evidence of cyclophosphamide-related urinary bladder cancer was observed, although the survival of these women may have been too brief to permit such an association to be documented.

Gastrointestinal Cancer:

Preliminary analysis of the relationship between dose of methyl-CCNU and risk of ANL/PL in 9 randomized clinical trials of gastric, colon and rectal cancer has suggested that a dose-response relationship exists.

Brain Cancer:

A survey of 2200 brain cancer patients treated with nitrosourea chemotherapy (primarily BCNU) revealed one ANL and 2 PL, a significant excess based on very small numbers and very short survival of cohort members. This provides some evidence to suggest that other nitrosoureas (i.e., not just methyl-CCNU) are leukemogenic in man.

Gestational Trophoblastic Neoplasms:

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

Hodgkin's Disease:

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

Childhood Cancer:

Analysis of the data collected in collaboration with the Late Effects Study Group regarding the occurrence of subsequent cancers in survivors of childhood malignancy continues. The initial analysis considered the risk of subsequent acute leukemia, and demonstrated a dose-response relationship between total amount of alkylating agent administered and leukemia risk. This leukemia excess is unrelated to dose of radiation therapy received. More recently, bone cancer as a second tumor has been considered. The risk of bone cancer rose in a linear fashion with increasing radiation dose to the tumor site. Independent of radiation therapy, alkylating agent exposure was associated with a 4-fold excess in risk of subsequent bone cancer. This latter finding represents the first observation of chemotherapy as a cause of solid tumors in man.

Breast Cancer:

Responsibility for studies of acute leukemia in women receiving adjuvant chemotherapy for carcinoma of the breast now rests with investigators in the Radiation Epidemiology Branch. Please refer to Project No. Z01CP05368-02 REB.

Miscellaneous:

A manuscript is now in preparation which describes in detail the histopathology of the acute leukemias and preleukemias identified in our various cohort studies. This is a collaboration between the expert hematopathologists who have been reviewing all case material and investigators from EEB and REB. Project staff contributed to the upcoming NCI Monograph celebrating the 50th anniversary of the Connecticut Tumor Registry by preparing chapters on malignancies occurring subsequent to lymphoid and hematopoietic tumors, cutaneous melanoma, and cancers of the brain, thyroid, connective tissue, bone and eye.

Significance to Biomedical Research and the Program of the Institute:

Studies of persons and groups at high risk of cancer lead to insights concerning risk factors and mechanisms for cancer. Results are significant because high risk groups identified through these studies can be monitored for early diagnosis, educated regarding their risk, and where possible cancer may be prevented by modification of lifestyle. These well-characterized high risk

groups are suitable for participation in interdisciplinary studies where laboratory approaches can be applied to provide fundamental insights at the molecular level concerning the mechanisms of their cancer risk. The burgeoning intramural collaboration between EEB and the Laboratory of Human Carcinogenesis, as exemplified by the study devoted to the biochemical epidemiology of lung cancer, heralds the direction in which our Program is moving.

Proposed Course:

The past year has been a time during which the Family Studies activity has re-grouped following major shifts in personnel, resources and priority mandated by our assuming responsibility for studies of AIDS and HTLV-I. The hereditary melanoma data base has comprised a continuing resource for new insights into the pathogenesis of cutaneous melanoma in man. Several unproductive avenues of investigation have been set aside, and the program has been re-focussed with the interdisciplinary research strategy still at the core of our efforts. This time-proven approach has been supplemented by a new and growing reliance upon the newest techniques of quantitative statistical genetics and an expansion of our interests to include population-based data sets which can prove genetically informative. Accordingly, the design and implementation of the nevoid basal cell carcinoma project has followed the research strategy that proved so successful in studying familial melanoma. This is a condition which is ideally suited to a carefully-orchestrated, clinical and laboratory research effort, one which makes use of the most modern techniques of molecular and cell biology and the clinical and genetic skills of project staff. In the coming year, this project will utilize a substantial fraction of project staff time and resources. The acquisition of POINTER, the current state-of-the-art method of segregation analysis, and the agreement of the CDC to share with us the CASH data base marks our entry into the arena of the large-scale population genetics of neoplastic disease. If this effort lives up to its potential, additional studies of this type will follow and the multiplex families identified will provide a resource of population-based kindreds suitable for more detailed laboratory investigation.

Studies of cytotoxic agents as risk factors for second primary cancers have been, and will undoubtedly continue to be, one of the most informative research areas in the Program. This project offers the unique opportunity to assess the carcinogenic effects of agents which are known or suspected carcinogens, in populations which have been carefully characterized, with time, duration and dose of exposure all known. The Late Effects Study Group data base, already the source of two major new observations, will continue to be explored for new associations and clues for subsequent investigation. The Stanford Hodgkin's disease study will provide the first information on the relationship between treatment amount and risk of subsequent leukemia, as well as the first reliable data on the incidence of cancers with longer latent periods. The ovarian cancer data base contains detailed information on cancers other than acute leukemia, and host data which may permit identifying unusually susceptible subsets of patients. Program-wide, the new initiative will be an expanded effort focussed upon acute leukemia in women receiving adjuvant chemotherapy for breast cancer. In view of the high prevalence of breast cancer, and the widespread use of

chemotherapy in relatively early stages of disease, this is currently the research question of greatest interest.

Publications:

Bale, S. J., Bale, A. E. and Levine, P. H.: The family study approach to investigating the role of genetic factors in nasopharyngeal carcinoma. In Levine, P. H., Ablashi, D. V., Pearson, G. R. and Kottaridis, S. (Eds.): Progress in Medical Virology, Vol 1. Boston, Martin Nijhoff (In Press).

Bale, S. J., Chakravarti, A., Ferrell, R. E. and Spence, M. A.: Possible heterogeneity in the PGP-HPA linkage. Am. J. Hum. Genet. 36: 808-814, 1984.

Bale, S. J., Chakravarti, A. and Greene, M. H.: Cutaneous malignant melanoma and familial dysplastic nevi: Evidence for autosomal dominance and pleiotropy. Am. J. Hum. Genet. (In Press)

Bale, S. J., Chakravarti, A. and Strong, L. C.: Aggregation of colon cancer in family data. Genet. Epidemiol. 1: 53-61, 1984.

Clark, W. H., Jr., Elder, D. E., Guerry, D., Epstein, M. N., Greene, M. H. and Van Horn, M.: Tumor progression - the events occurring within established primary melanoma. Hum. Pathol. (In Press)

Clark, W. H., Jr., Elder, D. E., Guerry, D., Epstein, M. N., Greene, M. H. and Van Horn, M.: A study of tumor progression - the precursor lesions of superficial spreading and nodular melanoma. Hum. Pathol. 15: 1147-1165, 1984.

Fraser, M. C. and McGuire, D. B.: Skin Cancer's early warning system. Am. J. Nurs. 84: 1212-1236, 1984.

Goedert, J. J., McKeen, E. A., Javadpour, N., Ozols, R., Pottern, L. M. and Fraumeni, J. F., Jr.: Polythelia and testicular cancer. Ann. Intern. Med. 101: 646-647, 1984.

Greene, M. H.: Cancer families - A resource for etiologic studies. In Castellani, A. (Ed.): Epidemiology and Quantitation of Environmental Risks in Humans from Radiation and Other Agents - Potential and Limitations. New York, Plenum Press (In Press).

Greene, M. H.: The dysplastic nevus syndrome-Precursors of hereditary and nonfamilial melanoma. In DeVita, V. T., Jr., Hellman, S. and Rosenberg, S. A. (Eds.): Important Advances in Oncology 1986, Philadelphia, JB Lippincott, (In Press).

Greene, M. H.: Epidemiologic studies of chemotherapy-related acute leukemia. In Castellani, A. (Ed.): Epidemiology and Quantitation of Environmental Risks in Humans from Radiation and Other Agents - Potential and Limitations. New York, Plenum Press (In Press).

Greene, M. H.: Hereditary melanoma and dysplastic nevi - 1985 status. Am. J. Dermatopathol. (In Press).

Greene, M. H.: Laboratory studies in patients with hereditary cutaneous melanoma and dysplastic nevus syndrome. In Elder, D. E. (Ed.): Pathobiology of Malignant Melanoma, Basel, Karger (In Press).

Greene, M. H. and Bale, S. J.: Genetic aspects of cutaneous malignant melanoma. Rec. Results Cancer Res. (In Press).

Greene, M. H., Clark, J. W. and Blayney, D. W.: The epidemiology of ovarian cancer. Semin. Oncol. 149: 274-284, 1984.

Greene, M. H., Clark, W. H., Jr., Tucker, M. A., Elder, D. W., Kraemer, K. H., Guerry, D., Witmer, W. K., Thompson, J., Matozzo, I. and Fraser, M. C.: Acquired precursors of cutaneous malignant melanoma - the familial dysplastic nevus syndrome. N. Engl. J. Med. 312: 91-97, 1985.

Greene, M. H., Clark, W. H., Jr., Tucker, M. A., Kraemer, K. H., Curtis, R. E., Elder, D. E. and Fraser, M. C.: Hereditary melanoma and the dysplastic nevus syndrome - The risk of cancers other than melanoma. Cancer Res. (In Press).

Greene, M. H., Clark, W. H., Jr., Tucker, M. A., Kraemer, K. H., Elder, D. E. and Fraser, M. C.: The high risk of melanoma in melanoma-prone families with dysplastic nevi. Ann. Intern. Med. 102: 458-469, 1985.

Greene, M. H., Elder, D. E., Acherman, A. B., Tucker, M. A. and Guerry, D.: Workshop on Dysplastic Nevi. In Veronesi, E., Cascinelli, N. and Santinami, M. (Eds.): Cutaneous Melanoma in 1985, Geneva, WHO (In Press).

Greene, M. H. and Wilson, J.: Second cancers following lymphatic and hematopoietic malignancies in Connecticut. Natl. Cancer Inst. Monogr. (In Press).

Kantor, A. F.: Calculation of HLA phenotype frequencies from two- and three-locus haplotype frequencies. Hum. Hered. (In Press).

Kraemer, K. H. and Greene, M. H.: Dysplastic nevus syndrome - Familial and sporadic precursors of cutaneous melanoma. Dermatol. Clinics 3: 225-237, 1985

McGuire, D. B.: Impact of hereditary melanoma on families. Cancer Nurs. 7: 451-459, 1984.

McGuire, D. B.: Preventive health practices and educational needs in families with hereditary melanoma. Cancer Nurs. 8: 29-36, 1985.

Pottern, L. M. and Blattner, W. A.: Etiology and epidemiology of multiple myeloma and related disorders. In Wiernik, P., Canellos, G., Kyle, R. and Schiffor, C. (Eds.): Neoplastic Diseases of the Blood and Blood-Forming Organs, New York, Churchill Livingstone, 1985, pp. 413-429.

Pottern, L. M., Brown, L. M., Hoover, R. N., O'Connell, K. J., Stutzman, R. E., Javadpour, N. and Blattner, W. A.: Testicular cancer among young men: The role of cryptorchidism and inguinal hernia. J. Natl. Cancer Inst. 74: 377-381, 1985.

Pottern, L. M. and Goedert, J. J.: Epidemiology of testicular cancer. In Javadpour, N. (Ed.): Principles and Management of Testicular Cancer, London, Thieme-Stratton (In Press).

Tollerud, D. J., Blattner, W. A., Fraser, M. C., Morris-Brown, L. M., Pottern, L. M., Shapiro, E., Kirkemo, A., Javadpour, N., O'Connell, K., Stutzman, R. E. and Fraumeni, J. F., Jr.: Familial testicular cancer and urogenital developmental anomalies. Cancer 55: 1849-1854, 1985.

Tollerud, D. J., Brinton, L. A., Stone, B. J., Toberman, J. K. and Blattner, W. A.: Mortality from multiple myeloma among North Carolina furniture workers. J. Natl. Cancer Inst. (In Press).

Tucker, M. A., Boice, J. D., Jr. and Hoffman, D. A.: Second cancer following cutaneous melanoma, and cancers of the brain, thyroid, connective tissue, bone and eye in Connecticut. Natl. Cancer Inst. Monogr. (In Press).

Tucker, M. A., Hartge, P. and Shields, J. A.: Epidemiology of intraocular melanoma. Rec. Results Cancer Res. (In Press).

Tucker, M. A., Misfeldt, D., Coleman, C. N., Clark, W. H., Jr. and Rosenberg, S. A.: Cutaneous malignant melanoma after Hodgkin's disease. Ann. Intern. Med. 102: 37-41, 1985.

Tucker, M. A., Shields, J. A., Hartge, P., Augsburger, J., Hoover, R. N. and Fraumeni, J. F., Jr.: Sunlight exposure as a risk factor for intraocular melanoma. N. Engl. J. Med. (In Press).

CONTRACTS IN SUPPORT OF THIS PROJECT

BIOTECH RESEARCH LABORATORIES INC (NO1-CP-21007)

Title: Laboratory Support for Processing and Storage of Biological Specimens from Persons at High Risk of Cancer.

Current Annual Level: $360,000

Man Years: 6.0

Objectives: To provide specimen processing and storage for a wide variety of biological materials obtained from persons at high risk of cancer.

Major Contributions: During the past year, 136,253 vials of biological

specimens from 40,256 individuals were received, processed and stored. Serum and lymphocytes were the primary materials handled. During the same interval, 56,926 vials of material from 36,600 individuals were distributed to the laboratories of collaborating investigators.

Proposed Course: Samples will continue to be collected, processed, stored and distributed according to quality control and processing guidelines, in providing critical support to Family Studies, AIDS, HTLV and other EEB projects.

FLOW LABORATORIES, INC. (N01-CP-21021)

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

Current Annual Level: $103,000

Man Years: 3.0

Objectives: To establish, maintain and develop a repository of skin fibroblasts and epitheliod cell lines from persons at high risk of cancer.

Major Contributions: Nearly 4100 cell strains have been collected to date. Fibroblasts have been grown in tissue culture to obtain DNA and RNA for various molecular studies.

Proposed Course: This procurement is in its final year. A new concept has been approved, and plans are now underway to re-compete this contract.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04411-09 EEB

PERIOD COVERED: October 1, 1984 to September 30, 1985

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

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

PI:	H. M. Hayes	Veterinary Medical Officer	EEB	NCI
Others:	R. N. Hoover	Chief	EEB	NCI
	L. W. Pickle	Statistician	EEB	NCI
	T. P. Cameron	Veterinarian	DCE	NCI
	K. P. Cantor	Epidemiologist	EEB	NCI

COOPERATING UNITS (if any) Dept. of Vet. Anatomy, OH St. Un. (G. P. Wilson, J. Burt); Dept. of Vet. Biol., Un. of Minn. (V. Cox); Depts. of Ped. and Epid., Un. of Wash. (T. Pendergrass); Epilepsy Branch, NINCDS (K. Milne)

LAB/BRANCH: Environmental Epidemiology Branch

SECTION: Environmental Studies Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.3	1.2	0.1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The continuing purpose of this project is to identify domestic animal models applicable to further research into the etiology of cancer and related disease in humans. As cases accumulate, it is likely that some types of spontaneous cancers in pet animals can be identified as representing the effects of low-level environmental exposure to carcinogenic agents. The frequency of cancer in these animals would serve as a warning of general environmental hazard(s) to people in the same locale. The topics of current investigation are: 1) environmentally influenced cancer in dogs relative to the level and type of industry in their county of residence (e.g., bladder, nasal, and oral cancers); 2) morbidity among pet dogs living in Michigan, potentially exposed to polybrominated biphenyls; 3) morbidity among military working dogs who had considerable exposure to Agent Orange; 4) the epidemiologic features of prostatic cancer in pet dogs; 5) a case-control study of malignant lymphoma in dogs relative to the use of herbicides and pesticides by their owners; and 6) equine oncology and teratology.

PROJECT DESCRIPTION

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

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

Objectives:

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

Methods Employed:

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

Major Findings:

1. A retrospective study of dogs seen at Michigan State University shows those diagnosed with primary neoplasms associated with polybrominated biphenyls (PBB) toxicity in laboratory studies (epithelial neoplasms of the liver, intrahepatic biliary tract and thyroid, and carcinomas of the rectum) are one year younger ($p<0.05$) at diagnosis in the period, 1978-1981, than those diagnosed prior to the PBB accident, 1969-1972. This finding is consistent with PBBs acting as a tumor promoter in the field, as it is in the laboratory. Similar data from 8 other U.S. veterinary universities did not show an age differential. Measurement of PBB body-burdens in Michigan dogs is proposed, as is an assessment of the factors associated with these neoplasms which may provide morbidity information before the first chronic human effects can be detected.

2. A case-control study of canine cryptorchism estimated a relative risk of 9.2 for developing testis neoplasia. Among dogs with inguinal hernia, the estimated relative risk was 4.2 for testis neoplasia. In high-risk closely related breeds of dogs, the relative risk of

cryptorchism was always inversely associated with adult size, suggesting genetically influenced maldescent may be related, in part, to physical size or the rate of growth of involved structures.

Significance to Biomedical Research and the Program of the Institute:

The chronic human health effects from environmental PBB exposure in Michigan are unknown. Surveys to date have not detected significant health changes. Since the life span of the dog is much shorter, as is the typical latent period for environmental effects, monitoring Michigan dogs may provide clues to possible problems in similarily exposed people.

The development of the genital system in dog and man are very similar. Each shows about the same risk of developing testis neoplasia if cryptorchid. The controversy continues as to whether the etiologic basis for developing neoplasia in the undescended testis involves exposure to abdominal body temperature. Dogs could be made surgically cryptorchid soon after birth and the effect of abdominal body temperature could be determined.

Proposed Course:

The methods employed and projects listed will be continued next year.

Publications:

Hayes, H. M., Jr.: Breed associations of canine ectopic ureter: A study of 217 female cases. J. Small Anim. Pract. 25: 501-504, 1984.

Hayes, H. M., Jr.: Epidemiologic features of 5,012 cases of equine cryptorchism. Equine Vet. J. (In Press)

Hayes, H. M., Jr., Cameron, T. P., Cantor, K. P. and Pickle, L. W.: Michigan pet dogs: a sentinel for the health effects of environmental polybrominated biphenyls? Fund. Appl. Toxicol. (In Press)

Hayes, H. M., Jr., Pickle, L. W., Wilson, G. P. and Milne, K. L.: The effects of ear-type and weather on the hospital prevalence of canine otitis externa. Am. J. Vet. Res. (In Press)

Hayes, H. M., Jr. and Wilson, G. P.: Canine hypospadias. Vet. Rec. (In Press)

Hayes, H. M., Jr., Wilson, G. P. and Burt, J.: Feline hip dysplasia: Incidence among asymptomatic pets. Vet. Rec. (In Press)

Hayes, H. M., Jr., Wilson, G. P., Pendergrass, T. W. and Cox, V. S.: Canine cryptorchism and subsequent testicular neoplasia: Case-control study with epidemiologic update. Teratology (In Press)

Wilson, G. P., Olson, L. E., Pickle, L. W., Hayes, H. M., Jr.: Canine Skull linear and volumetric morphometrics. Zentralbl. Veterinarnud. [c] (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04412-09 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Carcinogenic Effects of Therapeutic Drugs

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

PI:	R. N. Hoover	Chief	EEB	NCI
Others:	J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
	J. D. Boice, Jr.	Chief	REB	NCI
	M. H. Greene	Deputy Chief	EEB	NCI
	L. A. Brinton	Acting Chief, ESS	EEB	NCI

COOPERATING UNITS *(if any)* 28 BCDDPs, 3 Kaiser Foun. Res. Inst. (A. Glass, G. Friedman, H. Ziel); GW Univ. (L. McGowan); 5 Comprehensive Cancer Centers; Gorgas Memorial Institute (W. Reeves); Cancer Institute of China (B. Li); 10 SEER Centers; Mayo Clinic (G. Malkasian)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.0	1.0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☒ (a2) Interviews

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

The purpose of this project is to study the long-term health effects of therapeutic drugs as they may relate to carcinogenicity. Cohort studies of exposed groups are conducted, as well as case-control studies of selected cancer sites which involve lifetime drug use histories. Emphasis has been on the evaluation of various hormonal preparations, immunosuppressive drugs, and cancer chemotherapeutic agents. No general effects of thyroid medications or antihypertensive medications have been seen on breast cancer risk, but menopausal estrogens seem to increase the risk of benign breast disease. Ovarian cancer risk was found to be increased by use of progestins, but decreased by menopausal estrogen use. Cervical cancer was elevated among users of oral contraceptives, particularly for long-term users. Alkylating agents used for treatment of cancer and some non-neoplastic conditions were found to be associated with large excess risks of leukemia that were apparently dose related. Future analyses are planned to evaluate the effects of estrogenic preparations on a variety of female tumors and to assess, systematically, the role of adjuvant drug therapy among patients treated for a number of different cancers.

PROJECT DESCRIPTION

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

R. N. Hoover	Chief, Environmental Epidemiology Branch	EEB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
J. D. Boice, Jr.	Chief, Radiation Epidemiology Branch	REB	NCI
M. H. Greene	Deputy Chief	EEB	NCI
L. A. Brinton	Acting Chief, Environ. Studies Sec.	EEB	NCI
L. M. Brown	Epidemiologist	BB	NCI
G. Gridley	Health Statistician	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
D. A. Hoffman	Epidemiologist	REB	NCI
A. F. Kantor	Senior Staff Fellow	EEB	NCI
R. A. Kleinerman	Epidemiologist	REB	NCI
L. M. Pottern	Epidemiologist	BB	NCI
C. Schairer	Health Statistician	EEB	NCI
M. A. Tucker	Clinical Investigator	EEB	NCI

Objectives:

To study the long-term effects of therapeutic drugs in humans in order to identify drugs affecting risk of malignancy, and the characteristics and determinants of these risks; and to review what is known about the carcinogenic potential of drugs in order to identify those requiring study in humans.

Studies and Methods Employed:

1. A case-control study of breast cancer among mammography screening program participants has allowed an evaluation of the influence of thyroid medications and antihypertensive medications on the risk of breast cancer and menopausal estrogen use on the risk of benign breast disease. (See Project No. Z01CP04501-09 EEB.) Ongoing analyses are considering the relationship of menopausal estrogens and oral contraceptives to risk of breast cancer.

2. A study of the long-term effects of the immunosuppressive drugs is described in detail in Project No. Z01CP04401-09 EEB, "Immunologic Factors in Cancer Etiology."

3. A population-based, record-abstract, case-control study of 119 cases of breast cancer was conducted among women who had undergone a bilateral oophorectomy prior to breast cancer diagnosis and in control women who also had a bilateral oophorectomy, using data from a prepaid health plan to evaluate the risk of breast cancer associated with the use of replacement estrogens.

4. A population-based, record-abstract, case-control study of 510 cases of ovarian cancer and 604 controls from two prepaid health plans is currently under analysis to determine the relationship between the use of various therapeutic drugs and risk of this malignancy. The drugs being evaluated include estrogens, oral contraceptives, major tranquilizers, and other drugs affecting the pituitary-ovarian axis.

5. A case-control study, completed in the Washington, D.C. area, obtained home interviews from 350 ovarian cancer cases diagnosed in a 36-month period in 33 hospitals and from 350 age- and race-stratified hospital controls. Extensive information collected on oral contraceptives and menopausal estrogens will allow effects to be evaluated in relation to overall risk of disease, as well as to specific histologic subtypes. (See Project No. Z01CP04501-09 EEB.)

6. A case-control study of invasive and in situ cervical cancer has recently been completed; analyses are currently underway to assess the relationship of risk to use of oral contraceptives and other hormones (see Project No. Z01CP04501-09 EEB).

7. A pilot study demonstrated the feasibility of conducting a large case-control study of choriocarcinoma in the People's Republic of China. Of primary interest will be the assessment of oral contraceptives on development of choriocarcinoma and on promotion of hydatidiform mole to malignancy. (See Project No. Z01CP04501-09 EEB.)

8. A case-control study of in situ and invasive cervical cancer has been conducted in Panama. Interviews and sera were obtained from 156 of 169 surviving patients and from 309 age-matched neighborhood controls. This study allowed evaluation of the relationship of oral contraceptives to risk in conjunction with information on sexual behavior of study subjects. (See Project No. Z01CP04501-09 EEB.)

9. A large case-control study is currently underway in four Latin American countries to assess the reasons for excessive rates of invasive cervical cancer. Under investigation as possible etiologic factors will be oral contraceptives and other hormonal agents. (See Project No. Z01CP04501-09 EEB.)

10. Interviews with mothers of 271 testicular cancer patients treated at the NIH Clinical Center, Walter Reed Army Hospital, and Bethesda Naval Medical Center and 259 controls enabled an evaluation of the risk of testicular cancer associated with prenatal exposure to a variety of drugs, including CNS depressant drugs and DES. (See Project No. Z01CP04501-09 EEB.)

11. Three studies of the relationship between hormone use, histology specific benign breast disease, and breast cancer have been planned using the records of the Kaiser Foundation Medical Care Program. The first is a retrospective cohort study relating incidence rates of breast

cancer to (1) a number of clinically common subtypes and characteristics of benign breast disease and to (2) subclassifications defined on the basis of the Black-Chabon method of atypia scoring. About 2,500 women who had benign breast disease diagnosed by biopsy between 1948 and 1973 will be followed for occurrence of breast cancer (predominantly using Kaiser records) and will be compared to the expected numbers of breast cancers, using population rates. Secondly, a case-control study of benign breast disease and exogenous hormone use is planned. Cases will consist of women who had atypia levels >=4 (using the Black-Chabon method) and two samples of 50 women each who had scores of either 3, 1 or 2. Two controls per case will be selected from among women without benign breast disease. The third study will focus on hormone use subsequent to benign breast disease, the cases being women who had been previously identified with breast cancer subsequent to benign breast disease and controls being women with benign breast disease who remained within Kaiser as long as the cases, but did not develop breast cancer.

12. A case-control study in four U.S. cancer registries and in Denmark of 500 women who developed endometrial cancer as a second cancer following breast cancer therapy and matched controls has been completed. Detailed information was collected on medical histories and estrogen exposures, allowing the risk of endometrial cancer to be evaluated in relation to cumulative estrogen use. (See Project Nos. Z01CP4410-09 EEB and Z01CP05368-02 REB.)

13. To determine if an association exists between isoniazid and bladder cancer, as suggested by previous reports, data were analyzed from a national case-control study of 2,982 patients with bladder cancer and 5,782 population controls. (See Project No. Z01CP04501-09 EEB.)

14. A retrospective cohort study of approximately 3,000 women evaluated for infertility at the Mayo Clinic during 1935-1964 is nearing completion. Medical records have been abstracted to obtain demographic and medical details. Follow-up information has been obtained through personal contacts on subsequent events, including reproductive events, malignancies, and vital status. Analyses will be undertaken in the near future to assess the relationship of cancer risk to both the reasons for the infertility and the prescribed hormonal therapies.

15. An extensive program of studies are underway to assess, quantify and elucidate the determinants of the cancer risks associated with therapeutic exposures to cytotoxic drugs. This includes case-control evaluations of second primary tumors, cohort evaluations of cancer patients treated with different therapies, and the systematic monitoring of selected, informative clinical trials of various cancer treatments for long-term effects. This extensive program is described in detail in Project No. Z01CP04410-09 EEB, and also summarized in Project No. Z01CP05368-02 REB.

Major Findings:

1. Data from the Breast Cancer Detection Demonstration Project allowed evaluation of effects of thyroid disease and supplementation on breast cancer risk. A previous diagnosis of treated thyroid disease was not associated with an excess risk (RR=1.0), nor were any specific diagnoses, including hypothyroidism, hyperthyroidism, or goiter. Although based on limited numbers, women with untreated hypothyroidism or goiter had a significantly reduced risk of breast cancer (RR=0.3). Thyroid supplementation for non-disease reasons (primarily weight loss and fertility problems) was associated with a slight elevation in breast cancer risk (RR=1.2), but patterns of risk by duration or latency generally failed to provide evidence of causality.

   Other unpublished analyses reveal no association between breast cancer risk and either a diagnosis of hypertension or ever use of antihypertensive medications. However, long-term rauwolfia users did appear to experience some elevation in risk.

   Analysis of the relationship of estrogen replacement therapy and risk of benign breast disease revealed a significant association. The risk of benign breast disease rose with increasing years of use and with years since initial use (RRs=1.9 for 15 years of use and 1.6 for 15 years since first use). Among users of the conjugated estrogen Premarin, increased risks were found at all but the lowest dose.

2. Analysis of menopausal estrogen use among bilaterally oophorectomized women in the prepaid health plan showed no relationship of ever use with breast cancer risk. However, when additional measures of use were examined, those with 5 or more notations of use were at a significantly elevated risk (RR=2.1) and there was a significant trend toward increasing risk with more notations. Use specifically of conjugated estrogens was also associated with an increasing risk with more notations of estrogen use.

3. Preliminary analyses of the medical record study of ovarian cancer in prepaid health plans show a small (50%) but significant increase in ovary cancer among women with any mention of progestin use. This association increases to greater than 2-fold with increasing number of mentions in the medical record. Dose information needs to be examined in greater detail. Most of the women exposed to this type of drug had abnormal bleeding. In this data set, this condition was itself associated with risk of ovary cancer of the same magnitude as the drug association. These two findings may be inextricable in this data set. No association of ovary cancer was found with exogenous estrogen use, and oral contraceptives were slightly protective (though non-significant).

4. Unpublished analyses from the ovarian cancer case control study in Washington, D.C. show a reduced risk associated with use of menopausal estrogens.

5. Initial analyses of data from the U.S. cervical cancer study showed no relationship of risk with use of oral contraceptives (RR=0.8). However, the relationship was significantly confounded, particularly by the interval since last pap smear. Control for this variable as well as for sexual and sociodemographic factors increased the RR to 1.5, and showed that long-term users were at an 80-100% increased risk. Risks associated with long-term use of the pill were not substantially altered when those at unusual risk (users of barrier methods, non-contracepting women, and those with a history of abnormal pap smears) were excluded.

6. The case-control study of cervical cancer in Panama also provided evidence of an elevated risk for users of oral contraceptives. Users were at a significant 2-fold excess risk that was not substantially affected by controlling for sexual parameters.

7. Analysis of data from the testicular cancer study showed an elevated risk associated with prenatal exposure to CNS depressant drugs. Use of DES by subjects' mothers did not appear to affect risk.

8. Analysis of data from the case-control study of breast cancer patients who developed endometrial cancer indicated a significant risk associated with estrogen therapy. All known risk factors for endometrial cancer were also observed. The Danish series has been published separately.

9. Analysis of data from the population based study of bladder cancer showed no excess risk associated with medications used for tuberculosis treatment or prophylaxis.

10. The results of studies conducted to assess the carcinogenic hazards associated with the therapeutic use of cytotoxic drugs are described in detail in Project No. Z01CP04410-09 EEB.

Significance to Biomedical Research and the Program of the Institute:

Drug exposure has been one of the most fruitful areas for identification of carcinogens in humans and subsequent opportunities for preventive programs and insights into the biologic mechanisms in cancer etiology. In addition, studies of the long-term carcinogenic effects of antitumor drugs are an important part of the evaluation of the safety of treatment of various malignancies with these agents.

Proposed Course:

1. Further evaluations of the relationships between a number of drugs and the risk of breast cancer and benign breast disease will be undertaken using the data from the two case-control interview studies done in conjunction with the Breast Cancer Detection Demonstration Projects (see Project No. Z01CP04501-09 EEB for a more complete description).

2. The studies of ovarian cancers in prepaid health plans and in Washington, D.C. will be analyzed, and potential for other drug evaluations in the health plans will be assessed.

3. The proposed course for the extensive program of studies of cytotoxic drug exposures are described in detail in Project No. Z01CP04410-09.

Publications

Bennett, J. M., Moloney, W. C., Boice, J. D., Jr. and Greene, M. H.: Acute myeloid leukemia and other myelopathic disorders following treatment with alkylating agents. Blood (In Press)

Brinton, L. A.: The relationship of exogenous estrogens to cancer risk. In Mettlin, C. (Ed.): Cancer Prevention and Detection 7: 159-171, 1984.

Brinton, L. A., Hoffman, D. A., Hoover, R. and Fraumeni, J. F., Jr: Relationship of thyroid disease and use of thyroid supplements to breast cancer risk. J. Chronic Dis. 37: 877-883, 1984.

Brinton, L. A., Hoffman, D. A., Hoover, R. and Fraumeni, J. F., Jr.: Author's reply. J. Chronic Dis. 37: 891-893, 1984.

Ewertz, M., Machado, S. G., Boice, J. D., Jr. and Jensen, O. M.: Endometrial cancer following treatment for breast cancer: A case-control study in Denmark. Br. J. Cancer 50: 687-692, 1984.

Greene, M. H.: Epidemiologic studies of chemotherapy-related acute leukemia. In Castellani, A. (Ed.): Epidemiology and Quantitation of Environemntal Risks in Humans from Radiation and Other Agents - Potential and Limitations. New York, Plenum Press (In Press)

Greene, M. H., Harris, E. L. Gershenson, D. M., Boice, J. D., Jr., Malkasian, G. D., Jr., Melton, L. J. III, Dembo, A. J., Moloney, W. R. and Bennett, J. M.: Melphalan may be a more potent human leukemogen than cyclophosphamide. N. Engl. J. Med. (In Press)

Greene, M. H. and Wilson, J.: Second cancers following lymphatic and hematopoietic malignancies in Connecticut. Natl. Cancer Inst. Monogr. (In Press)

Hiatt, R. A., Bawol, R., Friedman, G. D. and Hoover, R.: Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer 54: 139-144, 1984.

Kantor, A. F., Hartge, P., Hoover, R. N. and Fraumeni, J. F., Jr.: Tuberculosis chemotherapy and risk of bladder cancer. Int. J. Epidemiol. 14: 182-184, 1985.

Trapido, E. J., Brinton, L. A., Schairer, C. and Hoover, R.: Estrogen replacement therapy and benign breast disease. JNCI 73: 1101-1105, 1984.

Tucker, M. A., Meadows, A. T., Boice, J. D., Jr., Stovall, M., Oberlin, O., Stone, B. J., Hoover, R. N. and Fraumeni, J. F., Jr.: Leukemia after therapy with alkylating agent for childhood cancer. N. Engl. J. Med. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04480-09 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Studies of Occupational Cancer

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

PI:	A. Blair	Chief, Occupational Studies Section	EEB	NCI
Others:	M. Alavanja	Special Assistant	E&B	NCI
	K. Cantor	Epidemiologist	EEB	NCI
	S. Hoar	Epidemiologist	EEB	NCI
	B. Miller	Epidemiologist	EEB	NCI
	R. Spirtas	Biostatistician	EEB	NCI
	P. Stewart	Industrial Hygienist	EEB	NCI
	T. Thomas	Epidemiologist	EEB	NCI

COOPERATING UNITS *(if any)* Univ. of MN (L. Schuman); Univ. of IA (P. Isacson); Univ. of KS (F. Holmes); NY State Dept. of Health (N. Vianna); U.S. Coast Guard (T. Haas); USDA (J. Teske); U.S. Air Force (S. Birch); Veterans Admin. (P. Legolvan); Univ. of LA (P. Correa), NIOSH (H. Amandus, W. Halperin)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Occupational Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
13.5	10.5	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.)*

Epidemiologic studies of occupational groups are conducted to identify and clarify the role of environmental factors in the origin of cancer. Potential for heavy and prolonged exposure, coupled with the availability of work history records, make occupational groups invaluable in epidemiologic investigations of cancer. Numerous occupational groups are under investigation. Completed during the past year were studies of 1) embalmers exposed for formaldehyde and other fixatives revealing an excess of leukemia and cancer of the brain; 2) professional artists exposed to paints and solvents, revealing high frequencies of deaths from cancers of the bladder, kidney, brain, colorectum, prostate, and breast; 3) textile workers where, unlike previous reports, the risk of prostate and colon cancer was not associated with employment in the textile industry; 4) workers in oil refineries where a case-control study using complete work histories uncovered no striking associations between brain cancer and particular work categories; 5) pattern makers where a screening program for colorectal cancer and polyps uncovered approximately a two-fold increase for cancer but no excess of polyps; 6) farmers showing chronic lymphocytic leukemia tended to be associated with cattle production while myeloid forms tended to be associated with corn, hog, and chicken production and pesticide and fertilizer use; 7) U.S. veterans where disease-specific mortality risks by occupation and industry provided clues for further research in occupational epidemiology; and 8) bladder cancer where elevated risks were noted among truck drivers that could not be attributed to smoking and other confounding factors. Other investigations under way include proportionate mortality studies of plumbers and foresters; cohort mortality studies of formaldehyde workers, anatomists, dry cleaners, furniture workers, shipyard workers, aircraft mechanics, potters, grain millers and handlers, and chemists; and case-control studies of leukemia, lymphoma, soft-tissue sarcoma, mesothelioma, and brain and lung cancer.

PROJECT DESCRIPTION

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

A. Blair	Chief, Occupational Studies Section	EEB	NCI
M. Alavanja	Special Assistant	E&B	NCI
W. Blot	Chief	BB	NCI
K. Cantor	Epidemiologist	EEB	NCI
J. Fraumeni	Associate Director	E&B	NCI
D. Grauman	Computer Systems Analyst	BB	NCI
R. Hayes	Expert	EEB	NCI
M. Heid	Technical Information Specialist	EEB	NCI
S. Hoar	Staff Fellow	EEB	NCI
R. Hoover	Chief	EEB	NCI
J. McLaughlin	Staff Fellow	EEB	NCI
B. Miller	Epidemiologist	EEB	NCI
J. Sontag	Special Assistant	E&B	NCI
R. Spirtas	Biostatistician	EEB	NCI
P. Stewart	Industrial Hygienist	EEB	NCI
T. Thomas	Epidemiologist	EEB	NCI
J. Walrath	Staff Fellow	EEB	NCI

Objectives:

To identify and evaluate groups at high risk of developing cancer because of contact with carcinogenic materials in the work environment. To develop methods and resources to further research opportunities in the area of occupational epidemiology.

Methods Employed:

Cancer patterns are determined through evaluation of persons employed in specific plants, industries, and occupations. Records from companies, unions, professional organizations, state health departments, and tumor registries are used to identify exposed populations. Estimates of level and duration of exposure are obtained from available industrial hygiene data or from monitoring programs associated with the study. Human tissues of fluids may be obtained to validate diagnosis, to obtain measures of effect dose, or to uncover precancerous lesions. Follow-up resources for cohort studies include the Social Security Administration, Office of Personnel Management, National Death Index, state motor vehicle bureaus, state vital statistics offices, city directories, and post offices. The cancer experience of study groups is usually compared to that of the general population (geographic-specific, if possible). Whenever possible, comparisons are made with industrial populations not exposed to the substance being evaluated.

Proportionate mortality studies are conducted when population data are unavailable. Case-control studies of persons with particular cancers are carried out in geographic areas where industries or occupations of interest are concentrated. Occupational, demographic, and other information may be obtained on study subjects by personal interview and/or from available employment records.

Major Findings:

1. A case-control of bladder cancer in New England uncovered an elevated risk among truck drivers (odds ratio OR=1.5). The relative risk rose to 2.3 among those employed as truck drivers for five or more years. The risk was greatest among men who began driving in the 1930s and 1940s (OR=2.6). Exposure to diesel fuel and exhausts had little affect on the risk of bladder cancer. Drivers reporting diesel exposures had an OR=1.8, while those lacking diesel exposures had an OR=1.5. These associations were unchanged after control for potential confounding factors including smoking and coffee drinking.

2. Analysis of causes of death among professional artists revealed an excess of leukemia and cancers of the bladder, kidney, brain, colorectum, and prostate among men. The excesses for leukemia and cancer of the bladder were particularly striking among painters, while the excess for prostate cancer was limited to sculptors. A reanalysis of data from the National Bladder Cancer Survey also noted an increased risk for bladder cancer among professional painters. Among women (particularly women painters), higher than expected proportions of cancers of the colon, rectum, lung, and breast were observed. These excesses may be due to pigments and dyes, solvents, metal fumes, and dusts used by professional artists in their work.

3. A previous study of embalmers and funeral directors in New York noted excess deaths from leukemia and cancer of the brain. A follow-up proportionate mortality study in California also noted excesses for these tumors (leukemia PMR=175 and brain cancer PMR=194). Although embalmers may come in contact with a variety of chemicals including formaldehyde, it was not possible to calculate exposure specific risks in this study. A review of epidemiologic studies of formaldehyde noted a consistent excess of leukemia and cancer of the brain among persons engaged in the preservation of biologic tissues (anatomists, pathologists, embalmers and funeral directors), but not among industrial workers. Among these professional groups simultaneous exposure may occur to a variety of chemicals including formaldehyde, glycerols, phenol and stains. A large study of industrial workers with detailed information on formaldehyde exposure is nearly complete and will clarify the role of formaldehyde in the origin of these tumors, but nested case-control studies among professional groups are needed to evaluate the role of other chemicals.

4. Previous studies have revealed an elevated mortality from leukemia and cancers of the brain and stomach among members of the Oil, Chemical, and Atomic Workers Union. Work histories of persons employed in the petrochemical industry who died from leukemia, brain cancer, or stomach

cancer were compared with those of persons dying from other causes in an attempt to identify occupational tasks associated with these tumors. No strong associations for brain cancer or leukemia risk were seen with any particular work category. Stomach cancer mortality was associated with employment in the processing of lubricating oils and paraffin wax.

5. Screening for colorectal cancer and polyps by flexible sigmoidoscopy among pattern makers uncovered a 2.6-fold excess of colon cancer. Exposure data were insufficient to link the excess to any specific characteristic of pattern making. Compared to other asymptomatic populations the proportion of pattern makers with polyps did not appear excessive. No association between colon polyps and employment characteristics was detected.

6. A study of female chemists detected a significant excess of suicide (Mortality Odds Ratio, MOR=5.4), and cancers of the breast (MOR=1.63), ovary (MOR=2.2), and lymphatic and hematopioetic system (MOR=2.2). The excesses for cancers of the breast and ovary were confined to persons never married which is consistent with known epidemiologic patterns. Lymphoma risk has been excessive in other studies of chemists in the U.S., Great Britian, and Sweden.

7. A case-control study of leukemia using death certificates was conducted in an attempt to identify histologic types of leukemia most strongly associated with farm practices. Chronic lymphatic leukemia was elevated among farmers from counties with large cattle inventories and with heavy dairy activity. Acute lymphatic leukemia and acute and chronic myeloid leukemia were more common among farmers residing in major corn-producing, hog and chicken raising, and pesticide and fertilizer using counties. Studies that obtain more detailed information from farmers by direct interview are nearing completion and will help clarify these associations.

8. The mortality experience of a nationwide cohort of 293,958 veterans was analyzed by occupation and industry to generate hypotheses in occupational cancer. Information from questionnaires provided data on tobacco use. Excesses of lung cancer among shipyard workers, truck drivers, and railroad workers are consistent with previous reports. Elevated risks for stomach cancer among carpenters, machinists, and steelworkers may reflect exposure to dusts and abrasives.

9. In collaboration with the Swedish National Board of Health and Welfare and the National Board of Occupational Safety and Health, analyses of linked data on occupation and industry and cancer incidence in Sweden are being performed. Initial studies revealed an association between sugar refinery work and mesothelioma and work in the leather industry and kidney cancer. An analysis of mesothelioma and occupation found significantly elevated risks among mechanics, plumbers, painters, pulp workers, tire workers, and workers in the shipbuilding and railroad equipment manufacturing industries.

10. Staff scientists also reviewed important current topics in occupational cancer including formaldehyde, silica and other nonorganic dusts and herbicides for publication or presentation at scientific meetings.

Significance to Biomedical Research and the Program of the Institute:

Studies of the cancer experience of working populations have provided much of the available information on chemical carcinogenesis in man. Occupational groups are extremely valuable in evaluating possible hazards to the general population because workplace exposures are often heavier and more well defined than exposures in the non-occupational environment. Studies of occupational groups may also provide information on the mechanism of action of chemical and physical carcinogens.

Proposed Course:

Work will continue on studies that are under way including plumbers exposed to glues, solvents, and plastic fumes; foresters exposed to pesticides; anatomists having contact with biologic preservatives and stains; dry cleaners exposed to perchloroethylene and other organic solvents; metal, wood, and plastic manufactures; aircraft mechanics routinely using organic solvents; grain millers exposed to ethylene dibromide and other fumigants; farmers exposed to herbicides and insecticides; and workers in the petrochemical industry. Data collection for a number of these projects is complete and reports are anticipated by the end of the year. A large cohort mortality study of approximately 30,000 workers exposed to formaldehyde included development of detailed exposure histories on all subjects and validation of these estimates through formaldehyde monitoring in each of the 10 participating plants. The cohort contributed approximately 700,000 person-years and nearly 5,000 deaths for analysis.

Population-based case-control studies of Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and soft-tissue sarcomas are nearing completion. Personal interviews of subjects in these studies will provide detailed information on their use of insecticides and herbicides and their contaminants to clarify the reported associations between pesticides and these tumors. Preliminary studies linking brain cancer and the petrochemical industry had lead to a case-control study of brain cancer centered in areas where the petrochemical industry is prevalent. Detailed work histories will be available to identify occupational exposures that may be involved in this association. A large case-control study of mesothelioma is under analysis to identify unsuspected sources of asbestos exposure and other agents that may play an etiologic role. Each case received a thorough review by a panel of expert pathologists to insure diagnosis consistancy among the reporting areas and to characterize histologic subtypes. New industrial populations may require epidemiologic investigation as leads are developed from clinical and laboratory observations. New studies will be initiated as high priority projects are developed. For example, we recently initiated a cohort mortality study of over 20,000 workers engaged in the production or use of acrylonitrile. This project involves the participation and collaboration of seven plants and includes industrial hygiene monitoring and bio-chemical epidemiology components to characterize environmental and effective exposures to acrylonitrile. In addition, findings from completed studies suggest areas where further research is needed to identify more accurately carcinogenic agents associated with the workplace and to better quantify the cancer risks. A nested case-control study of lung cancer among pesticide applicators

is under way to follow-up a mortality excess noted in a cohort study. Detailed information on tobacco use, work history, and pathology is being sought to clarify the cohort findings. Other such nested case-control studies will be initiated as provocative findings from ongoing projects become available. Special attention in all new projects will be focused on the issue of biochemical measurements to quantify effective exposures and to assess early biological damage.

Publications:

Bang, K. M., Tillett, S., Hoar, S. K., Blair, A. and McDougall, V.: Sensitivity of fecal hemocult testing and flexible sigmoidoscopy for colorectal cancer screening. J. Occup. Med. (In Press)

Blair, A., Hoar, S. K. and Walrath, J.: Comparison of crude and smoking-adjusted standardized mortality ratios. J. Occup. Med. (In Press)

Blair, A., Malker, H., Cantor, K. P., Burmeister, L. and Wiklund K.: Cancer among farmers: A review. Scand. J. Work. Environ. Health (In Press)

Blair, A., Walrath, J. and Malker, H.: Review of the epidemiologic evidence regarding cancer and exposure to formaldehyde. In Turoski, V. (Ed.): The Analytical Chemistry and Toxicology of Formaldehdye. American Chemical Society. (In Press)

Blair, A. and White, D. W.: Leukemia cell types and agricultural practices in Nebraska. Arch. Environ. Health (In Press)

Hoar, S. K., Bang, K. M., Tillett, S., Rodriques, M., Cantor, K. P. and Blair, A.: Screening for colorectal cancer and polyps among pattern makers. J. Occup. Med. (In Press)

Hoar, S. K. and Blair, A.: Agricultural and dioxin-related epidemiologic studies at the National Cancer Institute. Am. J. Ind. Med. (In Press)

Hoar, S. K. and Blair, A.: Case-control study of lymphoma and soft-tissue sarcoma: Association with herbicide exposure. In Cameron, T. P. (Ed.): Proceedings from the Third NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Studies. Bethesda, MD, NIH (In Press)

Hoar, S. K. and Blair, A.: Death certificate case-control study of cancers of the prostate and colon and employment in the textile industry. Arch. Environ. Health 39: 280-283, 1984.

Hoar, S. K. and Hoover, R.: Truck driving and bladder cancer mortality in rural New England. JNCI 74: 771-774, 1985.

Hoar, S. K., Santodonato, J., Cameron, T. P. and Kelsey, M. I.: Monographs on human exposures to chemicals in the workplace. J. Occup. Med. (In Press)

Hoar, S. K., Wilson, J., Blot, W. J., McLaughlin, J. K., Winn, D. and Kantor, A. F.: Second cancer following cancer of the digestive system in Connecticut. Natl. Cancer Inst. Monogr. (In Press)

Hoar, S. K., Blair, A., Holmes, F. F., Boysen, C. and Robel, R. J.: Herbicides and colon cancer. Lancet i: 1277-1278, 1985.

Malker, H. R., McLaughlin, J. K., Malker, B. K., Stone, B. J., Weiner, J., Ericson, J. and Blot, W. J.: Occupational risk for pleural malignant mesothelioma in Sweden, 1961-1979. JNCI 74: 61-66, 1985.

McLaughlin, J. K., Blot, W. J., Mehl, E. S., Stewart, P. A., Venable, F. S. and Fraumeni, J. F., Jr.: Petroleum-related employment and renal cell cancer. J. Occup. Med. (In Press)

Miller, B. A., Blair, A. and McCann, M.: Mortality patterns among professional artists: A preliminary report. J. Environ. Pathol. Toxicol. Oncology (In Press)

Spirtas, R., Hoar, S. K., Kaminski, R. and Rosenberg, H.: Aplastic anemia mortality and occupational exposures. In Stewart, W. F. (Ed.): Proceedings from the 1985 Public Health Conference on Records and Statistics. Washington, D.C., National Center for Health Statistics (In Press)

Sweeney, M. H., Walrath, J. and Waxweiler, R. J.: Mortality among retired fur workers: Dryers, dressers (tanners), and service workers. Scand. J. Work. Environ. Health (In Press)

Thomas, T. L., Krekel, S. and Heid, M.: Proportionate mortality among corn-wet milling workers. Int. J. Epiedmiol. (In Press)

Thomas, T. L., Stewart, P. and Blair, A.: Nonfibrous dust and cancer: Studies at the National Cancer Institute. In Goldsmith, D. and Winn D. (Eds): Proceedings of Silica, Silicosis, and Cancer: An International Symposium. Philadelphia, Praeger (In Press)

Thomas, T. L., Waxweiler, R. J., Crandall, M. S., White, D. W., Moure-Eraso, R. and Fraumeni, J. F., Jr.: Cancer mortality patterns by work category in three Texas oil refineries. Am. J. Ind. Med. 6: 3-16, 1984.

Walrath, J. and Fraumeni, J. F., Jr.: Cancer and other causes of death among embalmers. Cancer Res. 44: 4638-4641, 1984.

Walrath, J., Li, F. P., Hoar, S. K., Mead, M. W. and Fraumeni, J. F., Jr.: Causes of death among female chemists. Am. J. Public Health 75: 883-885, 1985.

Walrath, J., Rogot, E., Murray, J. and Blair, A. (Eds): Mortality Patterns Among U.S. Veterans by Industry and Smoking Status. NIH Publication No. 85-2747, Washington, D.C., U.S. Government Printing Office, 1985, 254 pp.

Walrath, J., Rogot, E., Murray, J. and Blair, A. (Eds): Mortality Patterns Among U.S. Veterans by Occupation and Smoking Status. NIH Publication No. 85-2756, Washington, D.C., U.S. Government Printing Office, 1985, 311 pp.

CONTRACTS IN SUPPORT OF THIS PROJECT

MASTER AGREEMENT ORDERS (NCI-CP-21019-65)

Title: Tracing Individuals for Environmental Epidemiologic Studies on Cancer

Current Annual Level: $873,983

Man Years: 3.0

Objectives: To provide specialized tracing services for epidemiologic studies conducted by the Epidemiology and Biostatistics Program using various record resources including credit bureau files, motor vehicle licenses, vital records, telephone directories and other publicly available lists, and a variety of other sources and resources.

Major Contributions: Over the past 12 months, 25 separate awards were made under this Master Agreement (MA). These are generally moderate to difficult subjects to trace. An overall average of 30 percent were successfully located; an average of 18 percent were located via credit bureaus, 35% via motor vehicle bureaus, and 44% by using a variety of other sources and resources. Success of tracing activities for individual projects depended on the information available concerning each subject's sex, and date of last known contact with the subject. Tracing was carried out on about 17,000 subjects. These not found by the initial method used other independent tracing methods until the NCI Project Officer decided that further tracing would not be economical or productive.

Proposed Course: Currently seven organizations are in the MA pool. The concept for a five-year extension of the project was approved by the DCE Board of Scientific Counselors in June 1984. Recompetition for entry of additional tracing organziation into the pool is under way.

SOCIAL SECURITY ADMINISTRATION (Y01-CP-10502)

Title: Determination of Vital Status and Personal Data of Epidemiological Study Cohorts.

Current Annual Level: $61,000

Man Years: 1.0

Objectives: To determine the vital status and obtain such demographic information as sex, race, and date of birth for members of epidemiologic study groups.

Major Contributions: This Interagency Agreement provides critical information needed for each retrospective cohort mortality study, namely the vital status of members of the study groups. This information is then used to obtain death certificates (in the event of death) or to conduct further follow-up efforts.

Proposed Course: The Project Plan for this effort has been approved through 1986, and it is anticipated that a new agreement will be developed for FY86 and that the work will continue according to the methodology outlined above.

WESTAT, INC. (NO1-CP-01020)

Title: Mortality Among Airplane Maintenance Workers.

Current Annual Level: $35,000 (Funds are provided by the Department of Defense through an Interagency Agreement.)

Man Years: 1.0

Objectives: To compare the mortality experience of workers exposed to solvents and other hazardous substances with that of internal and external control groups.

Major Contributions: Results are not yet available. Data collection is under way.

Proposed Course: Contract will terminate September 30, 1985.

TO BE AWARDED

Title: Support Services for Occupational Studies.

Current Annual Level: $949,990

Man Years: 20.0

Objectives: To provide technical, managerial, and clerical support for occupational studies conducted by the Environmental Epidemiology Branch.

Major Contributions: This contract will provide support for some 25 different projects. The contract this recompetition will replace made contribution to items 2-7 under "Major Findings" of this Intramural Research Report.

Proposed Course: Technical, managerial, and clerical support for occupational studies provided by this new award will continue until September 30, 1988.

SRA TECHNOLOGIES INC.

Title: Mortality Study of Workers Exposed to Acrylonitrile

Current Annual Level: $624,737

Man Years: 3.0

Objectives: To evaluate the mortality experience of workers exposed to acrylonitrile.

Major Contributions: Results are not yet available. Data collection is under way.

Proposed Course: Continue the contract until the planned expiration date of February 26, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04501-08 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Case-Control Studies of Selected Cancer Sites

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

PI:	R. N. Hoover	Chief	EEB	NCI
Others:	J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
	W. J. Blot	Chief	BB	NCI
	W. A. Blattner	Chief, FSS	EEB	NCI
	L. A. Brinton	Acting Chief, ESS	EEB	NCI
	T. J. Mason	Chief, PSS	EEB	NCI

COOPERATING UNITS *(if any)* 28 BCDDPs; 10 SEER Centers; Dept. of Hlth., NJ (R. Altman); Temple Un.; Walter Reed Hosp. (R. Stutzman); Beth. Nav. Med. Cen. (K. O'Connell); Wills Eye Inst. (G. Shields); G. W. Un. (L. McGowan); 2 Kaiser Med. Cen. (A. Glass, G. Friedman); Can. Inst. of China (B. Li); 5 Comp. Can. Cen.

LAB/BRANCH

Envionmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10.0	7.0	3.0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☒ (a2) Interviews

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

The purpose of this project is to investigate, in analytic studies, the etiologies of selected cancers. Specific cancer sites and hypotheses are selected for which the need for investigation is clear but which have been difficult to study elsewhere. Case-control studies either recently completed or in progress include studies of the following sites or types: breast cancer, childhood and adult bladder cancer, colorectal cancer, cutaneous T-cell lymphomas, non-Hodgkin's lymphoma, leukemia, multiple myeloma, nasal cancer, testicular cancer, mesothelioma, intraocular melanoma, ovarian cancer, cervical cancer and choriocarcinoma. The studies focus either on tumors that have not been studied analytically before (e.g., because of the rarity of the tumor) or on hypotheses that are difficult to assess (e.g., because of the prevalence of the exposure or the need to detect an effect at low levels of exposure). Since these studies are often the first or most thorough to date, they collect data on a wide range of exposures, usually from interviews and medical records.

PROJECT DESCRIPTION

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

R. N. Hoover	Chief	EEB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
W. J. Blot	Chief	BB	NCI
W. A. Blattner	Chief, Family Studies Section	EEB	NCI
L. A. Brinton	Acting Chief, Environ. Studies Sec.	EEB	NCI
T. J. Mason	Chief, Population Studies Section	EEB	NCI
L. M. Brown	Epidemiologist	BB	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
J. J. Goedert	Cancer Expert	EEB	NCI
G. Gridley	Health Statistician	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
S. K. Hoar	Staff Fellow	EEB	NCI
A. F. Kantor	Senior Staff Fellow	EEB	NCI
L. M. Pottern	Epidemiologist	BB	NCI
C. Schairer	Health Statistician	EEB	NCI
M. H. Schiffman	Staff Fellow	EEB	NCI
D. J. Tollerud	Research Associate	EEB	NCI
M. A. Tucker	Clinical Investigator	EEB	NCI
D. Winn	Senior Staff Fellow	BB	NCI

Objectives:

(1) To identify tumor sites for which there are a number of unusual demographic, laboratory or clinical associations indicating the necessity to evaluate a broad range of potential exposures. (2) To identify populations in which these in-depth case-control evaluations can be most efficiently carried out. (3) To design, conduct, and analyze these intensive case-control studies.

Methods Employed:

During this year the project has included 20 studies using the case-control method: 3 of breast cancer, 3 of bladder cancer, 1 of colorectal cancer, 1 of mycosis fungoides, 1 of non-Hodgkin's lymphoma, 1 of leukemia and non-Hodgkin's lymphoma, 1 of multiple myeloma, 1 of nasal cancer, 1 of testicular cancer, 1 of mesothelioma, 1 of intraocular melanoma, 2 of ovarian cancer, 3 of cervical cancer, and 1 of choriocarcinoma.

1. Breast cancer patients (1,554) identified by the Breast Cancer Detection Demonstration Project (BCDDP), women with benign breast disease (1,574), and normal screenees (1,391) were interviewed in their homes to collect information about risk factors for breast cancer and use of oral contraceptives, other exogenous estrogens, antihypertensive agents, thyroid medications, and major tranquilizers. Histological and clinical data were collected from BCDDP records. Analyses of these data are currently under way. (See Project No. Z01CP04412-09 EEB).

2. A continuation of the breast cancer study noted above has been completed. Approximately 2,500 breast cancer patients, identified from the BCDDP, equal numbers of women with benign breast disease and women with no breast disease, have been interviewed at home to collect information about a range of potential risk factors. These include the risk factors obtained in the initial survey, plus additional information on anthropometry, smoking, alcohol use, and consumption of methylxanthine-containing beverages. Histological and clinical data have also been obtained from BCDDP records. The data are currently being analyzed in conjunction with information obtained during the first phase of the survey.

3. In conjunction with the second phase of the BCDDP case-control study, an investigation is under way to evaluate the temporal effects of parenchymal patterns on risk of breast cancer. This study will focus on approximately 310 women whose breast cancer was detected on the fifth annual screening examination and their matched controls. Mammograms from the first, fourth, and fifth screening examinations will be read blindly by Dr. John Wolfe. The concordance of parenchymal patterns between examinations, as well as the predictability of patterns for subsequent breast cancer, will be assessed in relation to information on standard breast cancer risk factors.

4. A case-control study is currently under way in collaboration with the Atlanta SEER (Survival, Epidemiology and End Results) Center to evaluate the differences in the estrogen receptor status of breast cancer cases according to breast cancer risk factors and selected tumor characteristics. Included for study will be 557 interviewed breast cancer cases and 568 controls. Interview information was obtained in conjunction with the Cancer and Steroid Hormone Study conducted by the Centers for Disease Control.

5. A case-control study of childhood bladder cancer involving interviews with 30 cases and 90 controls was conducted in cooperation with investigators participating in the SEER Program to determine whether childhood bladder cancer is associated with pre- or postnatal exposures to known or suspected bladder carcinogens, such as artificial sweeteners and cigarette smoking.

6. All bladder cancer patients (4,000) who were diagnosed in 1978 in five states and five metropolitan areas were identified, and controls (7,000) were drawn from the general population of the 10 geographic areas. Subjects were interviewed in their homes to collect data about saccharin use, smoking habits, occupational history, sources of drinking water, hair dye use, coffee-drinking, and medical history. Histological data were collected from pathology reports.

   All bladder cancer patients (150) who were diagnosed in 1979 in greater Atlanta, and controls (150) from the general population, have been interviewed, following the protocol described above.

7. A case-control study of bladder cancer was conducted in New Hampshire and Vermont to look for environmental associations in both sexes. According to mortality rates for 1950-1969, New Hampshire has the second highest bladder cancer mortality rates for both white men and women among the 48 contiguous states. Vermont has similarly high rates, especially for white women. Project personnel identified 364 New Hampshire and Vermont residents who died from bladder cancer and 758 residents who died from other causes during 1975-1979. Successful in-person interviews with the next-of-kin of 89 percent of the study subjects were obtained. The interview consisted of questions about occupation, residence, smoking habits, and other aspects of lifestyle. The questionnaires and the death certificate abstracts have been coded and edited. Analyses are currently under way. Information has also been collected describing the type and location of business establishments in the leather, textile, and paper and pulp industries during the past 40 years.

8. A methodologic case-control study of colorectal cancer is focusing on "fecal mutagen level" as a possible risk factor. Fecapentaene, the newly-identified, potent fecal mutagen will be measured in all subjects in the study. The study is based at three Washington, D.C. hospitals. The effects on fecal mutagen level of diet, medical workup, surgery, and recovery will be determined in order to validate the subsequent case-control comparison. This project has been in progress for 3 months; a total of 100 subjects will be studied in the next two years.

9. A case-control study of cutaneous T-cell lymphomas (CTCL) is under way in a series of 300 patients who are being treated for CTCL at the Skin and Cancer Hospital of Temple University in Philadelphia, Pennsylvania. The study has been designed to determine whether there is an association between CTCL and several variables, many of which have in common exposures of the host to chronic antigenic stimulation. The influence of environmental agents such as carcinogens will also be explored.

10. Analysis of data from the case-control study of non-Hodgkin's lymphoma patients treated at the NIH Clinical Center was initiated. The study consists of complete information on 91 cases and 121 sibling controls regarding radiation exposure, occupational exposure, and past drug usage.

11. A case-control study of leukemia and non-Hodgkin's lymphoma has been undertaken in Iowa and Minnesota. Interviews were held with 600 leukemia patients, 600 lymphoma patients, and 1200 population-based controls. The interview focused on occupation, medical history, exposure to ionizing radiation, solvents, and pesticides, smoking, socio-economic status, and family history of cancer. Data from the interviews is complete and analysis is under way. (See Project No. Z01CP04480-09 EEB).

12. A death certificate study was undertaken in North Carolina to assess the relationship between employment in wood-related industries and risk of death from multiple myeloma. Sociodemographic and occupational information was abstracted off death certificates for 271 individuals dying from multiple myeloma and 858 persons dying from other causes, matched to the cases on sex, race, age, county of residence and year of death.

13. A case-control study of nasal cancer included 160 patients diagnosed at four hospitals in North Carolina and Virginia. Telephone interviews obtained from these patients or their next-of-kin and a series of 290 hospital controls, as well as death certificate controls, focused on occupational exposures, residential history, medical history, and smoking and alcohol usage.

14. A total of 271 testicular cancer patients treated at the NIH Clinical Center, Walter Reed Army Hospital, and Bethesda Naval Medical Center and 259 controls treated in those hospitals for other cancers were interviewed in the hospital or by telephone to collect information about their occupational and environmental exposures, medical history (undescended testis, groin hernia, childhood diseases), family history of genital tract abnormalities and testicular cancer, and personal habits. Mothers of subjects were also interviewed by telephone to obtain data on subjects' prenatal and perinatal history (birthweight, gestational age, exposure to medications, x-rays, alcohol and tobacco).

15. A case-control study of mesothelioma is under analysis. The data were collected as part of the Louisiana State University Lung, Stomach, and Pancreas Study. Forty case subjects and forty control subjects were given a standard epidemiologic interview. Data will be analyzed to examine factors other than asbestos exposure that might cause this rare tumor.

16. A case-control study of intraocular malignant melanoma was undertaken in collaboration with Wills Eye Hospital in Philadelphia. Data collection for the study has been completed. A total of 1,465 medical records were abstracted and 1,285 telephone interviews completed.

17. Ovarian cancer patients (350) diagnosed between 1978 and 1981 in 25 Washington, D.C. area hospitals, and women hospitalized for other conditions (350), were interviewed in their homes to collect information about medical, family, reproductive and menstrual histories, use of exogenous estrogens, contraception, occupation, and smoking. Pathology slides have been reviewed and questionnaires mailed to subjects' physicians to collect additional data.

18. A study of ovarian cancer from the medical records of two prepaid health plans included 510 cases and 604 controls. Data on medications, illnesses, and surgical histories were abstracted. (See Project No. Z01CP04412-09 EEB).

19. A case-control study of invasive and in situ cervical cancer has been conducted in conjunction with five of the Comprehensive Cancer Centers whose rates of these diseases are excessively high. Home interviews were obtained from 481 patients with invasive disease, 293 with in situ cancer, and with 801 population controls, matched to the invasive cases on race, age, and geographic area, and identified through random digit dialing techniques. Interviews focused on reproductive and menstrual history, sexual behavior, medical events, contraceptive usage, smoking and alcohol use, diet, and family history of cancer.

20. A case-control study of cervical cancer was conducted in Herrera Province, Panama, an area that had previously been demonstrated to have excessive disease incidence. Personal interviews were conducted with 156 patients and 309 age- and neighborhood-matched controls. Blood specimens were obtained from all study subjects and assays for herpes simplex virus type II performed.

21. To determine the reasons for their high rates of invasive cervical cancer, a large case-control study has been initiated in four Latin American countries--Colombia, Costa Rica, Mexico and Panama. The study will include approximately 800 women with invasive cervical cancer and 1,600 matched controls. Personal interviews will focus on reproductive and menstrual factors, sexual behavior, contraceptive use, smoking, medical history, diet, family history, and sociodemographic information. Blood and cervical scrapings will also be obtained to assess evidence of infectious agents. In addition to the females, this study will also focus on the role of the male in the etiology of cervical cancer. Male subjects will comprise the husbands of sexually monogamous female subjects. These men will be interviewed in conjunction with a brief clinical examination that will be oriented toward assessing genital hygiene, circumcision status and evidence of infection. Blood samples will provide further information on the role of infectious agents.

22. A pilot study involving interviews with 25 choriocarcinoma patients and 75 controls demonstrated the feasibility of conducting a full-scale study. This study is nearing completion and will include interviews with approximately 165 patients with invasive mole or choriocarcinoma, 165 with hydatidiform mole and 330 neighborhood controls. Personal interviews focus on reproductive history, medical events, family history, diet, and contraceptive behavior. (See Project No. Z01CP04779-09 EEB).

Major Findings:

1. Preliminary analyses of data from the second phase of the BCDDP Study showed no association between breast cancer risk and smoking, even when heavy exposures were considered. A relationship between methylxanthine consumption and risk of benign breast disease has also failed to be confirmed in this data set.

The BCDDP data also provided an opportunity for estimating the attributable risk for multiple risk factors. Using a newly developed and straightforward approach, it was determined that approximately 55% of the breast cancer in this screened population could be attributed to four risk factors: family history of breast cancer in a first degree relative, age at menarche, age at first livebirth, and number of previous biopsies for benign breast disease.

2. Analysis from the National Bladder Cancer Study showed that a family history of urinary tract cancer was related to an elevated risk of bladder cancer (RR=1.4), and the risks were higher among subjects with certain suspected environmental exposures. Leather workers employed before 1945 were shown to be at increased risk of bladder cancer, whereas those employed later were not.

   Unpublished analyses of the cigarette smoking histories revealed a decrease in risk associated with stopping smoking or switching from unfiltered to filtered cigarettes, after appropriate adjustment for the effects of duration of smoking.

   Recent, unpublished analyses indicate that males usually employed as truck drivers or deliverymen have a significant 50% increase in risk of bladder cancer. Overall, a significant trend in risk with increasing duration of truck driving was observed. This trend was particularly consistent for drivers first employed at least 50 years prior to diagnosis. Of these, truck drivers employed 25 years or more experienced a 120% increase in risk. Elevations in risk were also suggested for taxicab and bus drivers. These findings, coupled with experimental evidence of the mutagenicity and possible carcinogenicity of motor exhaust emission particulates, suggest a plausible role for motor exhaust exposure in human bladder carcinogenesis. Preliminary analyses also indicated increased bladder cancer risk for painters, motor vehicle drivers, railroad workers, metal machinists, metal workers, construction workers, lumbermen and wood workers.

   The relation between occupation and bladder cancer in women was examined and found to be similar to those previously observed among men. Increased risk was apparent for women ever employed as metal workers (RR=1.5). Within this occupational category, punch and stamping press operators had a significant trend in risk with increasing duration of employment; the relative risk for women employed five or more years was 5.6. Women employed as metal machinists also had an elevated risk (RR=1.4). A significant trend in risk with increasing duration of employment as a machine operator was observed. Nonsignificant elevations in risk were also apparent for painters (RR=1.5) and for hairdressers (RR=1.4). Painters employed at least five years had a RR of 3.0 and hairdressers employed at least 10 years had a RR of 1.5.

   Information from 1,000 water utilities in the study areas was collected and merged with residential histories to create a year-by-year profile of water quality for each respondent. Overall, there was no elevation

in risk for lifetime use of surface sources compared to nonchlorinated ground sources. Nonsmokers showed excess risks for the use of chlorinated surface sources, with a relative risk of 2.5 for those who used surface sources for at least 60 years.

3. Preliminary analysis of bladder cancers in childhood suggested no difference between cases and controls in early or prenatal exposure to artificial sweeteners.

4. Preliminary analysis of bladder cancer in New England suggested a relation between bladder cancer and tobacco, truck driving, textile work, and leather work. Longer duration of truck driving and textile work was associated with greater risk. Self-reported exposure to diesel fumes was associated with risk, but no dose response was seen. No association with pulp or paper mill exposure, coffee, or bracken fern was apparent.

5. Preliminary analyses of data from the mycosis fungoides study suggest an association with employment in the chemical and metal industries; exterminators, chemists and welders and solderers showed the highest risk. Occupational exposure to coal tar, pitch or creosote was not associated with increased risk.

6. Preliminary analyses of the case-control study of non-Hodgkin's lymphoma patients suggest positive associations with work in wood- and metal-related jobs and among professional and clerical workers.

7. The death certificate study of multiple myeloma revealed no association between risk and employment in the furniture industry. However, stratification by year of birth and age revealed a significantly elevated risk for furniture workers born before 1905 and dying before age 65 (RR=5.4). Unexpectedly, farmers were found to be at a significantly decreased risk of death from multiple myeloma (RR=0.6).

8. In the case-control study of nasal cancer, furniture workers showed an elevated risk, especially of adenocarcinoma. Cigarette smokers were at approximately a two- to three-fold elevated risk for squamous cell tumors. Elevated risks were also associated with occupational exposures to chromates and chemicals. In females, an excess risk was associated with employment in the textile industry, particularly for jobs involving dust exposure.

9. Analysis of the testicular cancer study showed an elevated risk for undescended testis that increased with increasing age at correction. The risk was highest for those men whose undescended testis was never corrected. No increased risk was observed for the normally descended testis. Only a slight risk was seen for men without an undescended testis who had an operation for groin hernia.

   Excess risks were seen for mumps orchitis and testicular trauma. No substantial risks were associated with childhood diseases, x-rays below the waist, venereal disease, or vasectomy.

Analysis of mothers' interviews revealed low birth weight, unusual bleeding or spotting, and x-rays to be risk factors for testicular cancer.

10. Analysis of the intraocular melanoma study showed elevated risks associated with birth in the south, sun bathing, sun lamp use, failure to wear eye protection in the sun, and freckles. These data suggest that sunlight exposure is an important risk factor for intraocular melanoma. Unpublished observations suggest a relation between hormonal factors and eye melanoma risk.

11. Data from the ovarian cancer study showed a weak negative relation between history of mumps and ovarian cancer risk and no relation between mumps and age at menopause. Analysis of greater parity and earlier age at first birth showed that the former exerted a strong protective effect but the latter exerted no effect on risk. Unpublished analyses also show a reduced risk associated with early surgical menopause.

12. Preliminary analyses of the U.S. cervical cancer data indicate that a major risk factor for invasive disease is the absence of regular screening, with those never having had a pap smear or those with 10 or more years since last pap being at a 5- to 6-fold excess compared to those screened more recently. In addition, multiple sexual partners and early age at first intercourse were predictive of risk. Long-term smokers were at excess risk, primarily of squamous cell tumors. A history of previous sexual diseases did not exert significant effects on risk, but few women reported positive histories for specific diseases.

13. The Panama study of cervical cancer showed that sexual promiscuity was uncommon, but that it exerted a major effect on risk, with those reporting four or more life-time sex partners being at a 4-fold excess risk compared to those reporting only one partner. First intercourse at a young age was common, but it failed to alter risk once number of partners was taken into account. Although serologic tests showed that a large proportion of the subjects had antibodies to herpes simplex type 2, there were no significant differences between the cases and controls.

Significance to Biomedical Research and the Program of the Institute:

The case-control methodology provides a rapid, relatively inexpensive, yet scientifically valid way of assessing the relationship between a disease and a wide variety of potential causes of that disease (occupational, general environmental, lifestyle, genetic, etc.). This method is the usual one first employed by epidemiologists to test hypotheses that have come from clinical observations, laboratory experiments, or from descriptive epidemiologic efforts. Because of the speed with which these studies can be performed and the wide variety of potential causes that can be assessed simultaneously, these studies often provide the first sound scientific evidence of a preventable cause of malignancy. The evidence can then be acted upon through educational programs or regulatory actions. As such,

this type of work is a key element in identifying preventable causes of malignancy in humans.

Proposed Course:

1. The studies of breast cancer, colorectal cancer, cervical cancer in Latin America, and choriocarcinoma will continue in the data collection phase during the next year. In addition, there are plans for continuing the ovarian cancer study in prepaid health plans to accrue more cases and examine the findings in a more recent time-frame.

2. The first and second breast cancer surveys in the Breast Cancer Detection Demonstration Project, the bladder cancer study in Atlanta, the non-Hodgkin's lymphoma study, the leukemia/lymphoma study, the intraocular melanoma study, and the studies of testicular cancer, mesothelioma, mycosis fungoides, bladder cancer in children, bladder cancer in New England, ovarian cancer, and cervical cancer have all completed data collection and will undergo additional analyses during the next year.

3. Evaluations of a number of tumor sites will be conducted to identify those tumors for which intensive case-control studies would be the most appropriate next step in evaluating potential etiologic hypotheses. Avenues for appropriately achieving these case-control evaluations will be explored. Planned is a case-control study to assess risk factors for cancer of the vulva and vagina. In addition, several case-control studies will be initiated to attempt to explain the reasons for the excessive occurrence of tumors among blacks, including cancers of the esophagus, pancreas, prostate, and multiple myeloma. A study of endometrial cancer is also planned to assess the relationship of diet and obesity to risk.

Publications

Bracken, M. B., Brinton, L. A. and Hayashi, K.: Epidemiology of hydatidiform mole and choriocarcinoma. Epidemiol. Rev. 6: 52-75, 1984.

Brinton, L. A. Current epidemiological studies: emerging hypotheses. In Peto, R., Zur Hausen, H. (Eds.): Banbury Report - Aetiology of Genital Cancer: Virological and Epidemiological Aspects. New York, Cold Spring Harbor Press. (In Press)

Brinton, L. A.: Epidemiology of trophoblastic neoplasia. In Bagshawe, K. D., Rice, J. and Brinton, L. A. (Eds.): Proceedings of the Second World Congress on Trophoblastic Neoplasms. Natl. Cancer Inst. Monogr. (In Press)

Brinton, L. A., Blot, W. J., Becker, J. A., Winn, D. M., Browder, J. P., Farmer, J. C., Jr. and Fraumeni, J. F., Jr.: A case-control study of cancers of the nasal cavity and paranasal sinuses. Am. J. Epidemiol. 119: 896-906, 1984.

Brinton, L. A., Blot, W. J. and Fraumeni, J. F., Jr.: Nasal cancer in the textile and apparel industries. Br. J. Indust. Med. (In Press)

Bruzzi, P., Green, S. B., Byar, D. P., Brinton, L. A., Schairer, C.: Estimating the population attributable risk for multiple risk factors using case-control data. Am. J. Epidemiol. (In press)

Cantor, K. P.: Epidemiological studies to estimate effects of low-level exposures. In Vouk, V. B., Butler, G. C., Hoel, D. G. and Peakall, D. B. (Eds.): Methods for Estimating Risks of Chemical Injury: Human and non-Human Biota and Ecosystems. Geneva, WHO, IPCS, Wiley and Sons, Inc. (In Press)

Cantor, K. P., Hoover, R,, Hartge, P., et al. Drinking water source and risk of bladder cancer: a case-control study. In Jolley, R. L., Bull, R. J., et al. (Eds.). Water Chlorination Environmental Impact and Health Effects. Cehlsea, Michigan, Lewis Publishing, Inc., 1985, pp. 143-150.

Goedert, J. J., McKenn, E. A., Javadpour, N., Ozols, R. F., Pottern, L. M. and Fraumeni, J. F., Jr.: Polythelia and testicular cancer. Ann. Inter. Med. 101: 646-647, 1984.

Hartge, P., Kantor, A. F. and Hoover, R. N.: Bladder cancer risk and pipes, cigars, and smokeless tobacco. Cancer 55: 901-906, 1985.

Hoar, S. K. and Hoover, R.: Truck driving and bladder cancer mortality in rural New England. JNCI 74: 771-774, 1985.

Kantor, A. F., Hartge, P., Hoover, R. N. and Fraumeni, J. F., Jr.: Familial and environmental interactions in bladder cancer risk. Int. J. Cancer 35: 703-706, 1985.

Lesher, L., Hartge, P., Hoover, R. and McGowan, L.: Ovarian cancer and age at first birth (letter). JNCI 74: 1361-1362, 1985.

Marrett, L. D., Hartge, P. and Meigs, J. W.: Bladder cancer and occupational leather exposure. Br. J. Ind. Med. (In Press)

Pottern, L. M., Brown, L. M., Hoover, R. N., Javadpour, N., O'Connell, K. J., Stutzman, R. E. and Blattner, W. A.: Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. JNCI 74: 377-381, 1985.

Pottern, L. M. and Goedert, J.: Epidemiology of testicular cancer. In Javadpour, N. (Ed.): Principles and Management of Testicular Cancer. New York, Thieme-Stratton (In Press)

Reeves, W. C., Brinton, L.A., Brenes, M.M., Quiroz, E., Rawls, W. E. and deBritton, R. C.: Case control study of cervical cancer in Herrera Province, Republic of Panama. Int. J. Cancer 36: 55-60, 1985.

Schiffman, M., Hartge, P., Lesher, L. P. and McGowan, L.: Mumps and postmenopausal ovarian cancer (letter). Am. J. Obstet. Gynecol. 152: 116-117, 1985.

Tollerud, D. J., Blattner, W. A., Fraser, M. C., Brown, L. M., Pottern, L., et al.: Familial testicular cancer and urogenital anomalies. Cancer 55: 1849-1854, 1985.

Tollerud, D. J., Brinton, L. A., Stone, B. J., Tobacman, J. K. and Blattner, W. A.: Mortality from multiple myeloma in North Carolina furniture workers. JNCI 74: 799-801, 1985.

Tucker, M. A., Shields, J. A., Hartge, P., Augsberger, T., Hoover, R. N. and Fraumeni, J. F., Jr.: Sunlight exposure as risk factor for intraocular malignant melanoma. N. Engl. J. Med. (In Press)

Wu, P., Brinton, L. A., Wang, W., Sung, H., Ershow, A., Li, J. and Blot, W.: Case-control study of choriocarcinoma in the People's Republic of China. In Henderson, B. E. (Ed.): Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin. Natl. Cancer Inst. Monogr. (In Press)

CONTRACTS IN SUPPORT OF THIS PROJECT:

SRA Corporation (NCI-CP-41027)

Title: Support Services to Provide Water Quality Data

Current Annual Level: $132,000

Person Years: 2.5

Objective: To provide technical, managerial, and computer support in gathering data from water utilities in conjunction with environmental epidemiology studies.

Major Contributions: Collection of historical water quality data is ongoing in the States of Florida and Louisiana, following site visits to State drinking water agencies by the project officer and contractor personnel.

Proposed Course: When data collection is completed, the water utility data will be merged with personal residential histories from case-control interview studies. These data will be used to evaluate cancer risk associated with drinking water source.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05128-06 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Diet and Nutrition in Cancer Etiology

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

PI:	Regina G. Ziegler	Expert	EEB	NCI
Others:	W.J. Blot	Chief	BB	NCI
	A.G. Ershow	Staff Fellow	BB	NCI
	R.N. Hoover	Chief	EEB	NCI
	L.W. Pickle	Health Statistician	EEB	NCI

COOPERATING UNITS *(if any)* Natl. Cen. for Hlth. Stat. (H. Barbano); Natl. Inst. on Aging (J. Huntley); CA Tum. Reg. (D. Austin); Un. of Hawaii (A. Nomura); Un. of South. CA (B. Henderson); Kaiser Hlth. Plan of OR (A. Glass); Kaiser Hlth. Plan of North. CA (G. Friedman)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.2	0.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☒ (a2) Interviews

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

Dietary exposures being assessed in human populations include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake, such as fat, vitamin A, carotene, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum vitamin A; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, esophagus, pharynx, oral cavity, lung, cervix, pancreas, stomach, larynx, and prostate and multiple myeloma. 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 lifestyles, such as Oriental-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 and the USDA Food Consumption Survey are being analyzed to test specific hypotheses, such as the relationship of age at menarche to diet, 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, and the correlation of fecal mutagens with colorectal cancer is being examined in human populations.

PROJECT DESCRIPTION

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

R. G. Ziegler	Expert	EEB	NCI
A. E. Blair	Chief, Occupational Studies Section	EEB	NCI
W. J. Blot	Chief	BB	NCI
L. A. Brinton	Acting Chief, Envir. Studies Section	EEB	NCI
L. M. Brown	Epidemiologist	BB	NCI
K. Cantor	Epidemiologist	EEB	NCI
A. G. Ershow	Staff Fellow	BB	NCI
R. Falk	Health Statistician	EEB	NCI
G. Gridley	Health Statistician	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
T. J. Mason	Chief, Population Studies Section	EEB	NCI
J. K. McLaughlin	Staff Fellow	BB	NCI
L. W. Pickle	Health Statistician	EEB	NCI
M. Schiffman	Staff Fellow	EEB	NCI
D. Silverman	Epidemiologist	BB	NCI
J. Wilson	Staff Fellow	REB	NCI
D. M. Winn	Senior Staff Fellow	BB	NCI

Objectives:

1. To assess in human populations specific hypotheses concerning the relationship of diet and cancer that have been suggested by biochemical, animal, clinical, and epidemiologic studies. Such hypotheses may concern food groups, food items, macronutrients or micronutrients, general nutritional status, food additives or contaminants, cooking or processing practices, biochemical measures related to diet, or anthropometric parameters. Cancer may be initiated, promoted, or inhibited by such exposures.

2. To test systematically for the existence of associations between diet and specific cancers and to generate hypotheses about the nature of any relationships detected.

3. To develop and utilize national nutrition data resources that might contribute to cancer epidemiology.

4. To develop and validate methods for nutritional epidemiology, including dietary questionnaires, protocols for laboratory tests, analytic approaches, and statistical techniques.

5. To elucidate the basic biology of carcinogenesis through studying the influence of diet on cancer in human populations.

Methods Employed:

A. Studies seeking to explain distinctive geographic patterns in cancer risk, such as those revealed by the U.S. cancer maps, and assessing nutrition as one of several possible reasons

1. A population-based case-control study of lung cancer was implemented, in collaboration with the New Jersey State Department of Health, in six clusters of New Jersey municipalities with elevated rates for white males during 1967-76. The study was supplemented with a dietary component designed to assess whether carotene, retinol, total vitamin A, or the broader related food groups, or a non-nutritional correlate, was associated with reduced risk. Vitamin A has been postulated to protect against cancer primarily on the basis of experimental studies of pharmacologic doses of retinoids. Carotene has been postulated to protect against cancer primarily because of its chemical properties and the responsiveness of serum carotene to daily diet. The few relevant epidemiologic studies have demonstrated less specific associations: high fruit and vegetable and/or dairy product intake is found among those at reduced risk of certain epithelial cancers.

   In the interview, usual adult frequency of consumption, prior to 1975, of 44 food items and a history of vitamin pill usage were collected. Interviews were completed for 763 white male lung cancer cases diagnosed in 1980-81 and 900 population controls of comparable age, race, and residence. Forty percent of the interviews were with next-of-kin.

2. A parallel case-control study of lung cancer with a dietary component was implemented, in collaboration with the University of Texas School of Public Health, in those Gulf Coast areas of Texas showing unusually high lung cancer mortality rates. Approximately 150 male and female lung cancer cases diagnosed in 1976-82 and 180 population controls of comparable age, sex, race, and residence--as well as 153 white male laryngeal cancer cases and 179 white male population controls of comparable age and residence--could be interviewed directly and were asked about diet. The usual frequency of consumption, four years earlier, of 42 food items and usual vitamin pill usage were collected.

3. The case-control study of lung cancer in New Jersey conducted during 1980-81 included primarily white men. Comparable population-based case-control studies of lung cancer were initiated among black men and white women in the high risk areas of New Jersey in 1982. The relative risks and exposure rates for the pertinent dietary factors will be compared for the three populations, and the ability of poor diet to explain the rapid rise in lung cancer among U.S. blacks will be evaluated. The dietary component of the interview, expanded to assess other nutrients possibly correlated with retinol and/or carotene intake, like vitamin C, includes the usual adult frequency of consumption of 59 food items and a history of vitamin pill usage. Approximately 300 black male and 900 white female cases of lung cancer are expected to be ascertained for the study.

4. A case-control study of lung, pancreas, and stomach cancer was initiated in 1979 in southern Louisiana in collaboration with Louisiana State University because of the relatively high mortality rates for these three cancers in this region. The study sample consists of approximately 1250 lung, 400 stomach, and 350 pancreatic cancer patients and an equal number of hospital controls, individually matched by age, sex, race, parish of residence, and hospital. Next-of-kin provided approximately 27 percent of the interviews. Information was collected on dietary patterns (usual adult frequency of consumption of 57 food items prior to disease), food preparation and storage practices, beverages consumed, spices used, and alcohol consumption.

5. The coastal region of South Carolina has high esophageal cancer mortality for men, especially black men. A hospital-based case-control study of esophageal cancer in males was started in 1982 in the Charleston area. Approximately 60 cases and 60 controls, similar with respect to age, race, and hospital of treatment, will be interviewed directly in the hospital. A next-of-kin component was begun in 1984. The next-of-kin of approximately 120 men who died from esophageal cancer and an age-race matched sample of approximately 240 men who died from other causes during 1977-81 will be interviewed. All study subjects were residents of an eight county area of coastal South Carolina at the time of their death. The dietary interview includes 63 food frequencies (usual adult consumption, disregarding any recent changes in diet), food cooking and preparation practices, ethnic food items, beverage use, alcohol consumption, and a supplemental vitamin history.

B. Studies primarily focused on nutritional hypotheses

6. A death certificate-based, case-control study of colorectal cancer was carried out in the three regions of Florida with high rates of in-migration from the Northeast and North Central states. The U.S. cancer maps had shown that colorectal cancer mortality rates for white men and women were lower in the South by about 50 percent than in the Northeast or North Central states, a reduction that could not be explained by differences in income or population density. Close examination of the age-specific cancer mortality rates for those counties in Florida where many Northerners move at retirement revealed that colorectal cancer rates in those counties were as low as in Southern counties of comparable population and did not rise toward the Northern rates at older ages. This study seeks to explore the characteristics of this apparent reduction in risk, quantify it, and to see whether it might be due to some change in lifestyle (e.g., eating more fruit and vegetables or drinking different water), or whether it might be due to the migrants being a self-selected healthy subset of Northerners. The final study population, drawn from the 1979 Florida mortality tape, consisted of 935 colon cancer cases, 165 rectal cancer cases, 845 controls dying of other cancers, and 496 controls dying of causes other than cancer; only whites were selected. Both control series were frequency-matched to the case series on age, sex, and usual county of residence. Next-of-kin were interviewed by phone. Questions focused on residential history; medical history; social, economic, and

demographic characteristics; and a few indicators of general dietary patterns (usual adult frequency of consumption of 11 food items, before and after migration to Florida).

7. A population-based case-control study of breast cancer in young Oriental-Americans was started in 1984 in Los Angeles, San Francisco, and Oahu; 630 Chinese, Japanese, or Filipino cases are expected to be or have been diagnosed during 1982-1986. When Oriental women migrate to the U.S., their low rates of breast cancer rise toward American rates over a period of several generations as they adopt a more Westernized diet. In this study population, diet should be sufficiently heterogeneous to permit the identification of the strong associations of diet with breast cancer risk that are presumed to exist. The study subjects will be 55 years or younger so that many of their mothers, as well as they, can be interviewed about their childhood and adolescent diet. Thus the hypothesis that diet is operative on breast cancer risk primarily during these two periods of the life span can be evaluated. This study will also permit evaluation in Oriental-Americans of the standard breast cancer risk factors and an estimation of the difference in Oriental and Caucasian breast cancer rates attributable to various risk factors. Serum will be collected from the cases, several months after diagnosis, and the controls for cholesterol, triglyceride, lipoprotein, tocopherol, retinol, carotene and selenium determinations. In order to study the interrelationships of ethnicity, dietary patterns, hormonal levels and disease, urine and serum will be collected for hormonal assays.

8. It has been noted in several longitudinal studies of heart disease that serum cholesterol levels were reduced among those who later developed cancer, particularly colon cancer. A cohort study of serum cholesterol levels and subsequent cancer at any site is being conducted among the 200,000 members of the Kaiser Health Plan of Northern California who participated in multiphasic screening, a much larger group than any cohort analyzed so far. The more detailed and accessible records of the Kaiser Health Plan of Portland are being utilized for a case-control study of colon cancer and serum cholesterol that will consider issues such as time elapsed between the cholesterol determination(s) and cancer diagnosis; medical reasons for the cholesterol determination; relationship of multiple cholesterol values, if available; and the exact site, staging, and outcome of the cancer.

9. A study is being designed, in collaboration with the Division of Cancer Treatment Clinical Oncology Program, to measure specific fecal mutagens and total Ames test mutagenicity in several populations at high risk of colon cancer and in matched healthy controls. The high-risk groups will be (1) people with a strong genetic predisposition to colon cancer (familial polyposis, Gardner's syndrome, and certain families with an autosomal dominant risk), (2) colon cancer patients who have recovered and needed only limited surgery, and (3) people suspected of colon cancer who have not yet undergone any diagnostic tests. The third group will offer the opportunity to monitor fecal mutagenicity, serum nutrient levels, and possibly other biochemical measures through the phases of

diagnosis, hospitalization, surgery, perhaps chemotherapy and/or radiation, and gradual recovery. Such a prospective study may resolve many of the questions that arise when biological samples are collected from cancer patients in a case-control study. Approximately 15 members of each of the three high-risk groups and an equal number of controls will be recruited. A standard epidemiologic interview will be given to each study subject, and brief dietary interviews will be administered at the times fecal samples are collected.

C. Analytic studies of special cancers or special populations where nutritional questions are part of the total justification for the study

10. A case-control study of invasive and in situ cervical cancer was completed in five Comprehensive Cancer Centers with especially large numbers of cervical cancer patients (Philadelphia, Chicago, Miami, Birmingham, and Denver). A total of 481 invasive cases, 293 in situ cases, and 801 neighborhood controls, matched by age and race to the cases, have been interviewed. This study will be the first to evaluate dietary exposures in a large number of patients with clearly invasive cervical cancer. Low intake of several micronutrients--vitamin A, carotene, folacin, vitamin C, and vitamin E--has been postulated to increase the risk of cervical dysplasia, cervical cancer, or cancer in general. The folacin hypothesis is specific for cervical cancer. Moreover, poor nutritional status may partially explain the predominance of cervical cancer in women of low socioeconomic status.

The dietary interview included 71 food frequencies and a supplemental vitamin history in order to estimate the usual adult intake of the micronutrients of interest and to characterize dietary patterns and nutritional status. To complement the dietary interview, blood samples are being collected with which to measure serum levels of retinol, carotene, vitamin C, folacin, and tocopherol and red blood cell folate, and possibly serum cholesterol and ferritin. In addition, serum will be stored for immunologic assays of relevant infectious agents, such as herpesvirus type 2, papillomavirus, and cytomegalovirus. Blood is being collected from the cases several months after completion of treatment, when appetite, diet, and metabolism have had an opportunity to revert to patterns existing prior to disease.

11. To test dietary, occupational, lifestyle, dental, and other hypotheses regarding risks for oral and pharynx cancer, a case-control study has been initiated in four areas of the United States: the state of New Jersey, Los Angeles (L.A.), San Mateo, and Santa Clara counties in California, and the Atlanta metropolitan area. Approximately 1500 cases will be ascertained over a 15-month period beginning January 1, 1984 from population-based cancer registries. Fifteen hundred controls will be ascertained either by random digit dialing techniques for cases diagnosed at ages less than 65 or through Health Care Financing Administration rosters for elderly cases. Additionally, in L.A. county

about 500 neighborhood controls will be sought. Interviews will be conducted in the homes of the study subjects; only a small proportion of the interviews will be conducted with a next-of-kin since relatively rapid case ascertainment procedures are being employed. Information on dietary patterns will include an extensive food frequency checklist (usual adult frequency), food preparation, special diets, vitamin supplements, height and weight, and alcohol intake. Dietary indices to be formed from the data include retinol, carotene, nitrites, and specific food groups (e.g., fruits and vegetables).

12. A large multicenter case-control study of pancreatic, esophageal, and prostate cancer and multiple myeloma among blacks and whites of both sexes is being developed. All of these cancers are more common among blacks than whites. Sufficient numbers of black cases will be ascertained to evaluate how the relative risks and exposure levels differ between the races for these cancers. Aspects of diet that will be assessed by interview include nutrient deficiency (esophageal cancer), patterns of fat consumption (pancreatic and prostate cancer), and coffee and methylxanthine intake (pancreatic cancer). Blood will be collected in order to measure selected micronutrients, lipids, and hormones in the plasma.

D. Studies to develop and utilize national nutrition data resources

13. HANES I, the U.S. Health and Nutrition Examination Survey conducted in 1971-74 by the National Center for Health Statistics, collected dietary, biochemical, clinical, and anthropometric information on a national sample of 23,000 people. Reliable predictors of age at menarche are being sought in the data on food group consumption, macronutrient intake, and anthropometry for the approximately 100 women between the ages of 12 and 18 examined in this study. In international correlation studies and in case-control studies, a young age at menarche is associated with an elevated risk of breast cancer. Internationally, a young age at menarche is also correlated with certain broad dietary patterns. It is possible that within the U.S. population young age at menarche may be an informative indicator of dietary patterns that promote breast cancer.

14. Using the HANES I 24-hour dietary recalls, individual food items were ranked by their contribution to total vitamin A intake for various age-sex-race-region subpopulations. The 1689 different food items reported were combined into 485 more inclusive food items, based on their mean vitamin A content per serving and their generic nature. Case-control interview studies examining the association between vitamin A and cancer at various sites have been hampered by the restricted time available for interview. In the past, interviews have included different abbreviated lists of food items, or even broad food groups, thus limiting the comparability of results.

15. In 1982-84 the Environmental Epidemiology Branch (EEB), in cooperation with the National Institute on Aging, other NIH Institutes, and the National Center for Health Statistics, traced and re-interviewed, if still living, the 14,000 adults examined 8-14 years earlier in HANES I. By collecting intervening cancer morbidity and mortality for this cohort, associations between dietary patterns prior to disease and the common cancers can be evaluated. As these people were traced, their social security numbers were obtained so that further cancer mortality could be monitored with the National Death Index. A comprehensive dietary section, designed to assess exposure to those food groups, food items, nutrients, additives, and cooking practices now suspected of being related to cancer, was drafted by the EEB and incorporated into the re-interview. Analysis of these new data should provide useful descriptive information on dietary practices and dietary variation within the U.S. In addition, the expanded dietary section should facilitate future analyses of diet and cancer relationships within this cohort.

    Follow-up of the HANES I cohort is now complete. Analyses underway focus on diet and prostate cancer, diet and lung cancer, and cancer morbidity and mortality associated with coffee drinking, artificial sweetener use, smokeless tobacco, and calcium and vitamin D intake.

16. Water-borne chemicals constitute exposures of interest in studies of cancer etiology and in risk assessment calculations. There are very scanty data, however, on actual age-and-sex-specific intake of drinking water that can be used in determining levels of exposure. Data from the 1977-78 USDA Food Consumption Survey will be used to estimate intakes of water from food and beverages on an age-, sex-, season-, and region-specific basis. Water drunk from the tap; used to make tea, coffee, and other diluted beverages; and added to food in cooking will be considered separately from ingested water deriving from sources outside the immediate locality (for example, the water in canned soda pop).

Major Findings:

1. In the study to identify vitamin A indicator foods, an index of vitamin A contribution [considering frequency of consumption, portion size, and vitamin A density (IU per 100 mg)] was used to rank the food items in various subpopulations. A comparison of these ranks identified certain fruits and vegetables whose relative contribution to vitamin A intake varied by sex-race group, season of interview, and region of the country. Age and poverty level had little effect on the food rankings. The major contributing foods for any subpopulation included both retinol (dairy products, liver) and carotene (certain fruits and vegetables) sources of vitamin A, and included items (e.g., mixed tomato dishes) not usually considered. The top 50 foods were adequate to classify, correctly, 80%-90% of the individuals into low, moderate, and high consumption categories.

2. In the study of lung cancer in Louisiana, fruit and vegetable intake was inversely associated with risk in whites and blacks of both sexes. Those in the lowest quartile of fruit and vegetable consumption in each sex-race group had from 1.5 to 1.9 times the risk of those in the highest quartile. Adjustment for alcohol and cigarette use and Cajun lifestyle did not markedly reduce these associations. No other consistent findings with diet were noted in all sex-race groups.

3. Diet was found to be the major determinant of stomach cancer risk in the Louisiana study. Fruit consumption was a strong protective factor for both races, with a risk for the highest quartile compared to the lowest quartile of consumers estimated to be 0.5 for whites and 0.3 for blacks. No additional effect due to total vitamin A, carotenoid, or retinol intake was seen after controlling for fruit intake. Consumption of smoked foods and homemade or home-cured meats increased the risk of gastric cancer for blacks, but not for whites. These findings suggest that differing dietary practices, perhaps food preparation methods, among whites and blacks may account for the very high gastric cancer rates seen for blacks in the area.

4. Preliminary analysis of the Louisiana pancreatic cancer data suggests that cigarette smoking, alcohol consumption, and pork intake may be responsible for the elevated mortality rates seen in the area, especially among whites. Fruit consumption also appears to be a protective factor.

5. In the case-control study of lung cancer among white men resident in six high-risk areas of New Jersey, the men in the lowest quartile of carotene intake had 1.3 times the risk of those in the highest quartile after adjusting for smoking. No increase in risk was associated with low consumption of retinol or total vitamin A. Intake of vegetables, dark green vegetables and dark yellow-orange vegetables showed stronger associations than the carotenoid index, with the smoking-adjusted risks of those in the lowest quartiles of consumption of these food groups reaching 1.4-1.5 times the risks of those in the highest quartiles. The protective effect of vegetables was limited to current and recent cigarette smokers, with the smoking-adjusted relative risks for low consumers reaching 1.7, 1.8, and 2.2 times the risks for high consumers for vegetables, dark green vegetables, and dark yellow-orange vegetables, respectively. The reduction in risk with vegetable intake was most apparent for squamous cell carcinomas, but it extended to adenocarcinoma and most other cell types when only current and recent smokers were analyzed. This protection among current and recent smokers is consistent with the model that vegetable intake prevents a late-stage event of carcinogenesis. Consumption of dark yellow-orange vegetables was consistently more predictive of reduced risk than consumption of any other food group or the total carotenoid index, possibly because of the high content of β-carotene, relative to other carotenoids, in this particular food group.

6. The relation of vitamin A supplementation to lung cancer was also analyzed in the case-control study of lung cancer among white males

resident in six high-risk areas of New Jersey. Vitamin A supplements were associated with a reduced risk (0.86) of lung cancer. Vitamin supplements, in general, were associated with a reduced risk of 0.84. No effect of daily vitamin A supplementation by duration was observed. The relative odds of disease in daily vitamin users compared to non-users by duration of use were 0.90 (one to two years), 0.82 (three to nine years), and 0.87 (10 or more years). Nor was any consistent relation noted between dose of vitamin A supplementation and outcome. Use of multiple logistic regression to control other influencing factors, including tobacco use and level of dietary carotene and retinol intake, did not alter these results.

7. Studies have also provided insight into certain methodologic issues in the field of nutritional epidemiology. A recent article in the American Journal of Epidemiology comparing frequency with more quantitative methods of obtaining dietary intake data was criticized in a Letter to the Editor. The criteria proposed for evaluating the equivalence of the two methods was shown to be overly restrictive and alternative methods of analysis were presented.

Significance to Biomedical Research and the Program of the Institute:

Specific foods and food groups, nutrient levels, general dietary patterns, overall nutritional status, cooking and storage practices, and consumption of food additives and contaminants are being recognized as possible causes of cancer. Certain diets and foods seem to initiate carcinogenesis, others seem to promote it, while still others seem to reduce cancer risk. The American people seek guidance on diets to minimize their risk of cancer, and Congress and the Executive Branch seek advice on what to advocate and/or regulate. Epidemiologic studies of diet and cancer can contribute to a rational basis for public policy and individual decisions. It is necessary to test and quantify in human populations those hypotheses about the role of diet in carcinogenesis that have resulted from animal studies, in vitro experiments, clinical observations, and descriptive epidemiology. In addition, exploratory nutritional epidemiology can suggest associations between dietary patterns and cancer, which then serve as the basis for further laboratory research and analytic epidemiology.

Proposed Course:

Analysis will continue on recently completed studies and will be started on studies where data are currently being collected. The recently completed studies include lung cancer among females and blacks in New Jersey, lung and laryngeal cancer along the Texas Gulf Coast; stomach and pancreas cancer in Louisiana; colorectal cancer among Florida migrants; male esophageal cancer in South Carolina; and invasive cervical cancer at five cancer centers. Now in the field are case-control studies of breast cancer among young Oriental-Americans and oral and pharyngeal cancer in the United States. The study of four cancers in blacks and whites will go into the field in FY 1986.

Additional emphasis will be placed on international studies since many of the provocative high risk areas identified within the U.S. by the cancer

maps have been investigated. Many of these studies will be conducted by the new Biostatistics Branch. International studies in high risk areas include the four case-control studies in China: esophageal cancer in Linxian, lung cancer among women in Shanghai, choriocarcinoma in Beijing, and stomach cancer in Shandong. An ambitious intervention trial of multivitamin supplements among 2000 individuals with esophageal dysplasia and 28,000 other individuals residing in the high risk county of Linxian is underway. Also, a large population-based, case-control study of stomach cancer is being designed for several provinces near Florence, Italy, where gastric cancer rates are among the highest in the world. A case-control study of cervical cancer in several Latin American cities, where incidence rates have not yet decreased as sharply as in the U.S., will assess diet as one of several possible explanations.

The results from the studies of colorectal cancer among Florida migrants, breast cancer among young Oriental-Americans, and fecal mutagens among groups with differential risk of colon cancer will determine the direction in which the nutrition research on these major cancers will go. If the death certificate-based study of colorectal cancer in Florida migrants shows a reduction in risk upon migration from the Northeast-North Central states to the South, and defines the demographics of the subpopulation in whom the risk reduction is greatest, an incident case-control study of colorectal cancer will be initiated in Florida. This study might use both Northern and Southern controls and might assay fecal mutagenicity and other biochemical measures of diet and nutrition.

If the case-control study of breast cancer in young Oriental-Americans shows a strong association of Western diet, measured by any dietary parameter, with risk and defines the period of life during which sensitivity to diet is most pronounced, an additional study will be initiated in Oriental-American populations. Dietary questions will be directed toward the relevant period of life to try to identify the characteristics of a Western diet that influence breast cancer risk. In the category of studies primarily focused on nutritional hypotheses, also under consideration is a large case-control study of endometrial cancer, a cancer for which there is strongly suggestive, but not direct, evidence of an association with a Western, high-fat diet.

Analytic studies of cancers of special interest will continue to include diet as a potential risk factor. The assessment of diet will be, to some extent, comparable from study to study so that any associations found can be said to be specific for the cancer site and not a function of the interview instrument, the method of analysis, or selective recall. If certain cancers have no persuasive associations with diet, that, too, will be reported. Currently being planned for the U.S. are analytic case-control studies of biliary tract, oral, pharyngeal, vaginal, and vulvar cancer. A national multi-center case-control study of pancreas, prostate, and esophageal cancer and multiple myeloma will be conducted among both blacks and whites to identify reasons for the unusually high rates for all four of these cancers among U.S. blacks. For the first three cancers, dietary patterns are considered a major risk factor. As the Branch's experience in developing

short, reliable interviews that can distinguish broad dietary patterns increases, more of the studies of cohorts and families of special interest will incorporate a brief dietary component.

HANES I will continue to provide data for descriptive, methodologic, and hypothesis-testing studies. Other national nutrition data resources becoming available include HANES II, similar to HANES I but conducted during 1976-80 on another large U.S. sample; HANES III, which was concentrated in Spanish-speaking areas of the U.S.; and the 1978 USDA Food Consumption Survey, which oversampled in Alaska, Hawaii, and Puerto Rico and collected 24-hour recalls over several consecutive days. The EEB will continue to collaborate with other Federal agencies in the design of national nutrition surveys, just as it has with the NCHS in the development of the HANES I follow-up and the HANES III instrument. Analysis of the data from the HANES I follow-up is now beginning; approximately 55 analyses involving HANES follow-up data have been proposed by members of the EEB.

Other methodologic and descriptive reports will be based on our experience in fielding and analyzing nutritional epidemiology studies. For example, the dietary interviews for the lung cancer studies, systematically designed by a nutritionist, should provide useful descriptive information on vitamin pill consumption among representative healthy adult men and women, and on the need to distinguish between seasonal and non-seasonal consumption of fruits and vegetables in order to develop reliable measures of the intake of such nutrients as carotene.

The analytic study of invasive cervical cancer was the first attempt by the EEB to introduce a biochemical component into a large case-control study. Even more complicated biochemical components are planned for the studies of breast cancer in young Oriental-American women and four cancers in blacks and whites. Results should provide guidance for incorporating laboratory measures into future nutritional epidemiology studies, clearly an important trend within Branch activities. In the fecal mutagen study selected serum nutrient levels will also be monitored through the stages of cancer diagnosis, treatment, and recovery to see to what extent serum nutrient levels in cancer cases are abnormal and in how many months, if ever, they revert to normal. Changes in appetite, anxiety, food availability (in a hospital), and metabolism, as well as actual surgery, radiation, and chemotherapy, could easily modify serum nutrient levels.

Publications

Correa, P., Pickle, L. W. and Fontham, E. T. H.: Cancer in Louisiana: Case-control studies of environmental determinants in high risk parishes. In Cameron T., Blackwood, I., Freas, N. and Olbrich, J. (Eds.): Proceedings of the Third NCI/EPA/NIOSH Collaborative Workshop. NIH, Bethesda (In Press)

Correa, P., Fontham, E., Pickle, L. W., Chen, V., Lin, Y. and Haenszel, W.: Dietary determinants of gastric cancer in south Louisiana. JNCI (In Press)

Correa, P., Pickle, L. W., Fontham, E. T. H., Dalager, N., Lin, Y., Haenszel, W., and Johnson, W. D.: The causes of lung cancer in Louisiana. In Mizzell, M. and Correa, P. (Eds.): Lung Cancer: Causes and Prevention. Deerfield Beach, FL, Verlag-Chemie International, 1984, pp. 73-82.

Pickle, L.: Re: A comparison of frequency and quantitative dietary methods for epidemiologic studies of diet and disease. Am. J. Epidemiol. 121: 776-778, 1985.

Pickle, L., Correa, P. and Fontham, E.: Recent case-control studies of lung cancer in the United States. In Mizell, M. and Correa, P. (Eds.): Lung Cancer: Causes and Prevention. Deerfield Beach, FL, Verlag-Chemie International, 1984, pp. 101-115.

Pickle, L. W. and Hartman, A. M.: Indicator foods for vitamin A assessment. Nutr. Cancer (In Press)

Ziegler, R. G.: Assessing diet in case-control studies of cancer. J. Toxicol. Clin. Toxicol. 21: 129-150, 1983-84.

Ziegler, R. G.: Epidemiologic studies of vitamins and cancer of the lung, esophagus and cervix. Natl. Cancer Inst. Monogr. (In Press)

Ziegler, R. G., Devesa, S. S. and Fraumeni, J. F., Jr.: Epidemiologic patterns of colorectal cancer. In DeVita, V. T., Jr., Hellman, S. and Rosenberg, S. A. (Eds.): Important Advances in Oncology, Vol II. Philadelphia, J. B. Lippincott (In Press)

Ziegler, R. G., Mason, T. J., Stemhagen, A., Hoover, R., Schoenberg, J. B., Gridley, G., Virgo, P. W., Altman, R. and Fraumeni, J. F., Jr. Dietary carotene and vitamin A and risk of lung cancer among white men in New Jersey. JNCI 73: 1429-1435, 1984.

Ziegler, R. G., Mason, T. J., Stemhagen, A., Hoover, R., Schoenberg, J. B., Gridley, G., Virgo, P. W. and Fraumeni, J. F., Jr.: Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. Am. J. Epidemiol. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05400-02 EEB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Epidemiology of Human T-Cell Lymphotropic Viruses; ATL, AIDS and Cancer

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

PI:	W.A. Blattner	Chief, Family Studies Section	EEB	NCI
Other:	R.J. Biggar	Senior Investigator	EEB	NCI
	J.J. Goedert	Cancer Expert	EEB	NCI
	J.W. Clark	Senior Medical Staff Fellow	EEB	NCI
	S.H. Weiss	Medical Staff Fellow	EEB	NCI
	E. Murphy	Medical Staff Fellow	EEB	NCI
	M. Melbye	Visiting Fellow	EEB	NCI
	D.L. Mann	Chief, Metabolic Epidemiology Section	LHC	NCI
	R.C. Gallo	Chief, LTCB	LTCB	NCI

COOPERATING UNITS *(if any)* Dept. of Pathol., Univ. of West Indies, Kingston, Jamaica (W.N. Gibbs); Gorgas Memorial Inst., Panama City, Panama (W. Reeves); Dept. of Surgery, USUHS (D.M. Strong); Biotech Laboratories (A. Bodner); Westat, Inc. (S. Durako); Div. of Hematology, Hershey Medical Center (M.E. Eyster)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.0	7.0	1.0

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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

A new family of retroviruses with potential as etiologic agents in the cause of human malignancies has been discovered. HTLV-I has been associated with a distinct form of T-cell leukemia/lymphoma (ATL). HTLV-III is the putative etiologic agent of the acquired immunodeficiency syndrome (AIDS) associated with Kaposi's sarcoma and certain forms of Hodgkin's and non-Hodgkin's lymphoma. A major focus of our research has been to characterize the relationship of this class of virus to human malignancy. Results of these studies document the close link between HTLV-I and ATL, its worldwide distribution, and tendency to be tightly clustered in close association with ATL. Modes of spread include sexual and household factors, transfusion, and possibly vector-borne transmission. Possible genetic susceptibility is also suggested. An indirect etiologic mechanism of carcinogenesis is also suggested for HTLV-I in B-cell chronic lymphocytic leukemia (B-CLL), and for HTLV-III in studies of Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma. A major focus of HTLV-III research has been on cohorts at high-risk for AIDS followed longitudinally since the very beginning of the AIDS epidemic. Results of these studies have documented major modes of transmission of HTLV-III in homosexual men (via receptive anal intercourse with multiple partners in high-risk areas), in hemophiliacs (via commercial plasma products), and in drug users (via frequent needle injections). They have also documented the progression from seroconversion to subclinical immunodeficiency, to clinical manifestations (e.g., lymphadenopathy), to AIDS. Comparison of these cohorts has shown that full-blown AIDS develops in 5-20% of HTLV-III positive individuals over 32 months of follow-up. These results provide the foundation for undertaking in-depth analytic studies of these retrovirus exposure variables to better quantify these risks and the cofactors which determine the clinical outcome of exposure.

PROJECT DESCRIPTION

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

W. A. Blattner	Chief, Family Studies Section	EEB	NCI
M. H. Greene	Deputy Chief	EEB	NCI
R. J. Biggar	Senior Investigator	EEB	NCI
J. J. Goedert	Cancer Expert	EEB	NCI
D. L. Mann	Chief, Metabolic Epidemiology Section	LHC	NCI
J. W. Clark	Senior Medical Staff Fellow	EEB	NCI
S. H. Weiss	Medical Staff Fellow	EEB	NCI
E. Murphy	Medical Staff Fellow	EEB	NCI
D. Winn	Staff Fellow	BB	NCI
R. N. Hoover	Chief	EEB	NCI
D. J. Tollerud	Medical Staff Fellow	EEB	NCI
S. J. Bale	Staff Fellow	EEB	NCI
M. Melbye	Visiting Fellow	EEB	NCI

Objectives: To develop clinical and epidemiologic strategies for identifying the role of retroviruses in human disease. Studies are aimed at quantifying the distribution and determinants of retroviral infection in various populations and to quantify the determinants of disease, especially malignancies and the acquired immunodeficiency syndrome (AIDS) associated with one of a growing number of distinct isolates of such retroviruses. An interdisciplinary approach involving the collaboration of laboratory bench scientists and clinically oriented epidemiologists is employed to maximize etiologic insights and pathobiologic understanding. In this context, the ultimate object of this project is to exploit the model system offered by retroviruses for understanding fundamental mechanisms of human cancer causation through multidisciplinary epidemiologic studies.

Methods Employed: Protocols for study of high risk populations are developed by Section professionals in conjunction with Branch epidemiologists and clinical and laboratory collaborators. Questionnaires, abstract forms, and field study manuals are developed and tailored for the particular project and reviewed by the Branch Technical Evaluation of Projects and Technical Evaluation of Questionnaires Review Groups for scientific merit and compliance with Federal study requirements. Where appropriate, biospecimens are collected on all study subjects. These materials are then assessed to quantify retroviral exposure by serologic, tissue culture, and/or molecular techniques; and for measuring a variety of immunologic, genetic, immunogenetic, and other parameters related to viral exposure and disease outcome and/or susceptibility. Laboratory methods employed by collaborators include ELISA, immunofluorescence assay and radioimmune precipitation assays for viral antibodies and antigens, tissue culture of viable cells for virus isolation, cloned virus analysis for studying virus integration and expression, cytogenetic analysis including *in situ* hybridization for retroviral genomes, imunogenetic analysis including HLA typing by serologic

and molecular biologic techniques, in vitro immunologic analysis, quantitation of lymphocyte subsets and tumor phenotype by FACS and immunoperoxidase techniques, and molecular analysis of immunoglobulin and T-cell receptor gene rearrangement. Clinical techniques include medical history and physical examination of study subjects to determine extent and stage of disease and associated features. Epidemiologic techniques involve both descriptive and analytic approaches, including case/control and cohort analyses, and studies of family and household clusters. Statistical analytic approaches include analysis of variance, relative risk determination, trend analysis, linear and logistic regression, and statistical-genetic analyses including tests of linkage and segregation.

Background: With the discovery of the first human retrovirus, HTLV-I, and the emergence of the acquired immunodeficiency syndrome as a major U.S. public health problem, Family Studies Section personnel have embarked on a comprehensive series of clinical, laboratory, and epidemiologic investigations. Two project areas encompassing these activities were previously defined as "Human T-Cell Leukemia Virus (HTLV)" and "Acquired Immunodeficiency Syndrome (AIDS)." With the recent discovery of HTLV-III, a member of the human T-lymphotrophic retroviral family, as the etiologic agent of AIDS, the activities of these project areas have converged and new project titles created (see below). Since these activities are closely related in objective and are distinct from those of Family Studies, these projects have been defined as a new EEB project area under the direction of the Chief, Family Studies Section.

PROJECT 1: HTLV-I and Adult T-Cell Leukemia/Lymphoma

The discovery of the first human retrovirus, HTLV-I, by the Laboratory of Tumor Cell Biology (LTCB) of NCI has given new impetus to the hypothesis that viruses cause some human cancers. The objective of this project is to undertake a series of epidemiologic, clinical, and experimental studies aimed at defining the epidemiology of HTLV-I infection and its role as a cause of human cancer.

HTLV-I is the first true human retrovirus. Unrelated to any known animal virus, HTLV-I is an exogenous human retrovirus demonstrable in malignant T-cells of certain patients with T-lymphoproliferative malignancy, as well as from virally infected, clinically normal individuals. The Section became involved in collaborative studies with the LTCB in the spring of 1981. By applying epidemiologic principles, a broad range of clinical, etiologic, genetic, and experimental studies have been implemented whose results have played a key role in defining the association of HTLV-I with adult T-cell leukemia/lymphoma (ATL). In addition, Section staff developed quality control, assay standardization approaches, and quantified measures of sensitivity and specificity.

Relationship of HTLV-I to Human Disease:

When the Section undertook this project, the relationship of HTLV-I to human

malignancy was poorly characterized. Our studies led to the recognition of HTLV-I as a marker for ATL outside of the endemic areas in Japan and the recognition that the Caribbean area is a major HTLV-I endemic area. Based on these early insights, it was hypothesized that a single clinicopathologic entity, which closely resembled or was identical to ATL, was associated with HTLV-I. A series of parallel clinical and epidemiologic studies in several locales has been undertaken to extend our understanding of the spectrum of HTLV-I-associated lymphoid malignancies.

ATL in the United States:

An ongoing project involves the continued ascertainment of HTLV-I positive leukemia/lymphoma cases ascertained in the U.S. The purpose of this project is to extend observations made preliminarily on a handful of U.S. ATL cases and to determine the frequency of occurrence and clinicopathologic correlates. Well over 30 cases have now been ascertained and characteristic features of hypercalcemia, cutaneous involvement, leukemic transformation, Ann Arbor Stage IV presentation, and short survival have been confirmed. Epidemiologic analysis of the positive U.S. cases confirmed that they are significantly younger (median age 43) compared with peripheral T-cell lymphoma (median age 62), are more likely to be either southern (33%) or foreign born (40%), and black (66%) but with an equal male to female ratio. A special future focus is on cases in Japanese-Americans in Hawaii where 3 cases have recently been recognized, 2 among first generation Hawaiian born Japanese whose only apparent exposure to the virus is through the contact in their home environment. Studies of clinical staging, natural history and treatment (conducted with physicians from the Division of Cancer Treatment), have shown the utility of HTLV-I antibodies as a marker identifying a subset of non-Hodgkin's lymphoma patients in whom metabolic abnormalities and unexpected sites of involvement can be anticipated. Under a collaborative arrangement with the Division of Cancer Treatment, an aggressive treatment regimen is being developed enrolling cases ascertained through various epidemiologic studies.

HTLV-I in the West Indies:

A major focus of Section research activities involves epidemiologic studies of HTLV-I in the Caribbean region in collaboration with investigators at the University of West Indies campuses in Jamaica and Trinidad-Tobago. In prior years, a pilot survey of lymphoreticular malignancies in Jamaica documented the utility of HTLV-I antibodies as a marker for a particular subset of lymphoreticular malignancies with ATL-like features and confirmed that a substantial portion of all adult lymphoid malignancies are associated with HTLV-I. Of the total of 96 non-Hodgkin's lymphomas, 54% were HTLV-I antibody positive. Detailed clinical and pathologic analysis of these cases has shown that the vast majority have features of ATL, with leukemic phase, hypercalcemia, and cutaneous involvement being particularly prominent. These studies have helped to define better the spectrum of HTLV-I associated leukemia/lymphoma and have demonstrated cases lacking features of "classic" ATL but with antibody and monoclonally integrated proviral DNA of HTLV-I in

tumor cells. In contrast, on clinical grounds Jamaican HTLV-I antibody negative NHL cases generally lack ATL features, although occasional cases have some features, but without the same pattern of clinical progression. Integrated virus is also lacking in these cases. Histopathologically, HTLV-I positive cases have more frequent nuclear pleomorphism, although some HTLV-I negative cases share this feature. With the implementation of the Jamaica research contract, on-site analysis of tumor phenotype with monoclonal antibodies has confirmed th mature T-cell nature of such cases. Survival of HTLV-I positive cases is poor, particularly among those with hypercalcemia. An HTLV-I associated immunodeficiency state is suggested by the occurrence of more infectious complications in the positive as compared to negative cases. In support of this is the unusual occurrence of crusted scabies in some cases, and the observation of disseminated viral warts and virally associated penile cancer in situ in another case. During this year, the molecular analysis of Jamaican non-Hodgkin's lymphoma cases for HTLV-I integrated genomes documented the presence of integrated viral DNA in all positive cases and the absence of viral RNA expression in fresh tissue. Of particular interest were 2 cases with features suggestive of ATL who were virus-antibody and proviral-DNA negative, and some cases lacking features of ATL but with otherwise typical non-Hodgkin's lymphoma who were proviral and antibody positive. Ten cases of HTLV-I-associated non-Hodgkin's lymphoma have been analyzed from Trinidad, revealing that they have the features of ATL similar to those seen in other areas of the Caribbean and Japan.

A major ongoing focus of the epidemiologic analysis of these cases is a multicenter (Jamaica, Panama, and Trinidad-Tobago) case-control study of hematologic malignancies. The protocol for this project involves a comprehensive questionnaire and multidisciplinary laboratory approach aimed at defining parameters associated with leukemogenesis. Thus, a detailed questionnaire documents lifestyle and health variables, while the laboratory protocol focuses on characterizing cases by immunologic, cytogenetic, and virologic methods.

B-CLL and HTLV-I in Jamaica

Among 30 chronic lymphocytic leukemia cases, six (20%) were HTLV-I antibody positive, a rate higher than that of the corresponding normal population. In the few cases tested so far, all have been B-cell chronic lymphocytic leukemia (B-CLL). In two cases, an HTLV positive T cell line was established and was positive for integrated viral DNA, while the corresponding malignant B-cells from the same patients were HTLV-I viral genome negative. Sophisticated hybridoma technology was applied and the immunoglobulin rescued from malignant B-cells of these cases appears to react to viral or virus-infected cellular antigens. In one, the viral encoded p24 antigen of HTLV-I is selectively detected while the nature of the antigen detected in the second case is not fully characterized but may be virus related. Of interest in the first case is the recognition that the anti-p24 antibody detects an epitope cross-reactive with the p24 of HTLV-II and -III documenting the distant relatedness of these various classes of virus. A role for virally induced T-cell immunologic purturbation predisposing to B-cell malignancy is theoretically

possible in these cases, and experimental studies are under way to further explore these relationships. The observation that 3 of 15 cases of myeloid leukemia are positive is likely to reflect the fact that such cases may have been previously transfused, although other mechanisms whereby virally-induced myeloid lymphokine production plays a role in this process must also be considered in light of the finding of HTLV-I antibodies in myeloid leukemia cases from Japan and South Africa.

Surveys of Lymphoid Malignancies in Other Geographic Locales:

Serosurveys to evaluate the prevalence of HTLV-I in lymphoreticular malignancies in various geographic locales have documented viral positive cases in Nigeria, Israel, Taiwan, Colombia, United Arab Emirates, Okinawa and numerous other centers in Japan. Most of these HTLV-I antibody-positive cases have shared features of the sentinal disease ATL, that we have helped to characterize. A detailed case report of two patients from Nigeria documented that one case had classical features of ATL including hypercalcemia, pleomorphic cellular morphology, aggressive clinical course, and T-cell phenotype. A second case had an aggressive form of CLL.

Among a small series of cases from Cali, Colombia, South America, three black patients with features of ATL were identified, and all were found to have been born and lived in the low altitude, heavy rainfall, coastal area, raising the possibility of regional clustering. This hypothesis will be further pursued by a systematic regional study.

In summary, our clinical, epidemiologic studies have (a) demonstrated that the "sentinal disease" associated with HTLV antibodies in a population is ATL; (b) shown that clusters of HTLV-related ATL occur in the Caribbean, the United States, South America, and elsewhere, in addition to southwestern Japan; (c) characterized the clinical features and natural history of the disease, to alert physicians to the staging and prognostic significance of HTLV-I antibodies in their patients, and (d) suggested previously unrecognized indirect mechanisms for HTLV-I leukemogenesis.

Epidemiology of HTLV-I Infection:

West Indies: Recently in Jamaica a study of 926 persons including patients without hematologic malignancies seen at the University of West Indies in Kingston, a population of normal blood donors, and a childhood school survey, showed an overall HTLV-I antibody prevalence of 5.4%. This prevalence increases with age, with a peak prevalence of 20%, with an approximately equal male to female ratio and only a slightly higher rate in females older than 40 as compared to males. This is in contrast to Japan where the rate in females over the age of 40 greatly exceeds that in males. There was no obvious geographic clustering within Jamaica, consistent with the widespread distribution of ATL cases as well. In another study, preliminary analysis of a historic population-based survey of 87 individuals over the age of 65 from one geographic area does suggest

that there is a higher prevalence in females than in males in this group with an overall seroprevalence of 30%. Interestingly, other factors which correlated with antibody positivity in the historic cohort were low body weight, low weight to height ratio, and self-reported arthritis. Further analysis of this data is currently in progress.

A prospective survey of mothers and their offspring vaccinated for measles is under analysis to evaluate HTLV-I household transmission and the question of whether HTLV-I infection influences *in vivo* immune response to new antigens.

A major epidemiologic focus is a large island-wide serologic survey aimed at screening approximately 10,000 individuals. This study, initiated in collaboration with the Jamaica Ministry of Health, will develop an unbiased estimate of antibody prevalence in the normal 18-55 year old population. The study population will consist of all persons attending mandatory health clinics in each Jamaican parish because of employment in the food industry. The study is designed to evaluate geographic variation in the antibody prevalence in Jamaica, and in the future will serve as the basis for identifying a cohort of HTLV-I antibody positive and negative individuals for a case-control study of risk factors for infection and for determining "intermediate" health outcomes of viral infection in healthy individuals.

Other surveys are under way to extend knowledge of the possible geographic variation in HTLV-I seroprevalence in different locales of the Caribbean region. Currently under analysis is a cohort of 2,000 sera collected as part of a hepatitis survey in Trinidad-Tobago. This study provides the opportunity for evaluating risk factors for positivity by occupation, race, and sex and relationship of positivity to other infectious diseases. Of particular interest in this population is the fact that the population is equally divided racially between blacks and Asians and to date, all ATL cases in Trinidad-Tobago have occurred in persons of African ancestry. Preliminary analysis of the data from this cohort suggest that the HTLV-I antibody prevalence in the population is approximately 5%, similar to that seen in Jamaica and Panama.

A historic household survey of Barbados and St. Lucia, collected in the early 1970s by Dr. Alfred Evans of Yale Medical School, is being tested to investigate the seroprevalence in these populations, and it may be possible to trace study cohort members for retesting to determine health outcomes and seroconversion/seroreversion. A serosurvey of Turks and Caicos conducted by the Caribbean Food and Nutrition Institute is underway with specific plans to collect additional epidemiologic data and sera of interest to HTLV-I testing. An ongoing collaborative study in Haiti with the Cornell Medical School, aimed primarily at studying the epidemiology of AIDS, also provides an opportunity for investigating risk factors for HTLV-I as well; and sera from lymphoreticular neoplasms are also being collected for HTLV-I testing. Preliminary data from a small serosurvey of Puerto Rico document a relative absence of HTLV-I in that population, an observation that may suggest geographic difference in seroprevalence.

Panama: A collaborative analysis of various populations in Panama encompassing over 2500 individuals has been undertaken. Preliminary analysis demonstrates an overall prevalence rate of 5.9%. Unlike Jamaica, the prevalence rate by age is rather uniform, ranging between 5% and 8% without clear age specific rise. There was no significant difference in antibody prevalence between males and females. However, there does appear to be a geographic gradient in antibody prevalence ranging from approximately 1% in the southern region of the country, to 5% in central Panama, to 10% in the northern part of the country which neighbors Costa Rica. Epidemiologic features of the various Panamanian populations under study have been investigated. There was no correlation between income and education and antibody positivity, while in a small sampling, preliminary analysis suggests that the rates of positivity are increased as a function of household crowding. HTLV-I prevalence appears to increase with increasing number of lifetime sexual partners, supporting the hypothesis that male-to-female sexual transmission occurs. The finding of a high proportion of positives in persons with recurrent herpes zoster-like illnesses suggests a possible immunosuppressive role for HTLV-I which deserves further evaluation.

HTLV-I cross-reactive antibodies have been found in approximately 50% of 60 wild caught new world monkeys indicating the possible presence of a closely related virus in these monkeys. Lymphocytes for viral culture are being collected from primates from this region to determine the nature of the primate virus and its relationship to human and old world monkey HTLV-I-like retroviruses.

Venezuela: Preliminary results of surveys of sera from various geographic areas in Venezuela indicate prevalence rates ranging from less than 1% to over 12%. Although the populations sampled were not strictly comparable, there appeared to be some regional variation, suggesting a possible association the distribution of arthropod-borne diseases coincident with HTLV-I antibody prevalence. The titer of HTLV-I antibody increased with age, suggesting that re-exposure to the virus or continued proliferation of viral-infected cells provides ongoing antigenic challenge, while the more or less uniform prevalence by age group suggests that new infections or seroconversions in this population are rare.

Africa: A survey of populations from southern and western Africa demonstrated broad geographic differences in their rates of positivity. The highest rates were observed in equatorial Africa, but the populations in this survey were not exactly comparable, so these data must be viewed as preliminary. Furthermore, a high rate of non-specific reactivity was noted, due possibly in some part to the co-existence of cross-reactive retroviruses in the region, as well as a documented confounding of test results due to hypergammaglobulinemia. Very high rates of positivity in relatively young aged study subjects were noted, approaching 25% in a small sampling from Ibadan, Nigeria. Surprisingly, the proportion of HTLV-I seropositive cases among non-Burkitt, non-Hodgkin's lymphoma, and cases with ATL-like features was approximately 30% in contrast to the reported 50 to 60% occurrence in newly diagnosed cases in Jamaica and southern Japan. These data raise the

possibility of a different natural history for HTLV-I infection in this population, a hypothesis to be evaluated in the coming year.

In a community-based survey in Ghana, a similarly high rate in younger individuals and increasing prevalence with age were noted. When urban and rural populations were compared, there were no clear distinguishing features of lifestyles which correlated with antibody prevalence, although poor social class was almost universal. There was a correlation between HTLV-I reactivity and prevalence and titer of antibody against malaria, consistent with either a vector-borne pattern or non-specific polyclonal B-cell activation associated with HTLV-I infection. Systematic population-based surveys are now underway in Tanzania, Kenya, Zambia, and Nigeria, and follow-up studies are being planned in Ghana.

Okinawa: Studies of patients with ATL and normal controls have confirmed that Okinawa is a highly HTLV-I endemic area with rates of positivity approaching 40% in some older normal population age groups. Results of one study have confirmed the strong association with ATL, a non-significant female excess in older aged study subjects, an age dependent rise in antibody prevalence and titer, and a strong link of seropositivity to strongyloides infection. Studies in Okinawa suggest the possibility of HTLV-I seroconversion among U.S. servicemen stationed there, a finding with possible long-term health consequences that is being further evaluated.

Hawaii: A collaborative study has been established with the Kuakini Medical Center in Honolulu to evaluate HTLV-I in Hawaiian Japanese. Seroprevalence in Okinawa born migrants to Hawaii was 20%, virtually identical to the 19.6% rate in similarly aged first generation Hawaiian born Japanese of Okinawan descent. In contrast, the virus was virtually absent in migrants and first generation Hawaiian born from an HTLV-I non-endemic area of Japan indicating that Hawaii per se is not an HTLV-I endemic area. Seroprevalence increased with years of residence prior to migration from Okinawa suggesting environmental co-factors in Okinawa itself which contribute to risk for HTLV-I infection. The offspring of migrants had a significant increase in seropositivity with age in the absence of an obvious environmental source for exposure raising the possibility that virus infection can exist in a latent phase possibly from birth, with subsequent apparent seroconversion reflecting an actual reactivation of latent virus infection.

Other Surveys: HTLV-I antibodies have been detected in normal persons from Sardinia, Singapore, Egypt, Alaska, and in non-lymphoid cancer patients from Tunisia. A survey of over 150 laboratory workers, who are a group at high risk of exposure to HTLV-I has documented only one positive: a Jamaican-born glass washer whose antibodies to HTLV-I on stored sera antedated the discovery of HTLV-I and T-cell tissue culture work by over 10 years. A detailed analysis of migrant populations to the United Kingdom documented a close correlation of HTLV-I antibodies to ATL cases, the long latency between migration and ATL development and the familial clustering of HTLV-I antibodies.

Family Studies of HTLV-I Infection:

A study of the distribution and determinants of HTLV-I infection in families, especially in close relatives of HTLV-positive ATL cases is underway. To date, 25 families from the U.S., Japan, and West Indies have been ascertained. The prevalence of HTLV antibodies in close family members is 3 to 4 times greater than that seen in the corresponding normal population in each region. Antibody positivity has been documented in the mothers of all ATL cases tested to date. Testing for immunogenetic markers and cytogenetic abnormalities is currently under way. Preliminary analysis of the HLA data in ATL family members in relationship to HTLV-I antibody suggest that there is no association between HLA type (including the B5 cross-reactive group) and disease once a person is infected, although the numbers are small. In the family setting, the data do suggest the possibility of linkage between a genetic marker of the major histocompatibility locus and an assumed autosomal dominant HTLV-I susceptibility locus (although the lod score is only .803 and, therefore, more data are needed before a final conclusion can be made). Further studies involving the development of suitable HLA reagents to pursue these questions in an HTLV endemic area, Jamaica, are currently under way.

HTLV-I in Blood Donors:

The pattern of HTLV distribution is similar to that of hepatitis B. We are investigating the risk of blood-borne HTLV transmission by: (a) defining the prevalence of HTLV serum antibodies in blood bank donors; and (b) establishing the rate of HTLV-I seroconversion in recipients of blood products from HTLV seropositive donors. Recently, large-scale blood bank surveys involving over 1500 U.S. donors have been completed. Of 571 predominantly Caucasian blood donors in Burlington, Vermont, 1% were positive, with the rate in persons over the age of 30 being 1.45%. In Birmingham, Alabama, of 639 donors 2.2% were positive, with the rate in persons over the age of 30 being 3.8% suggesting a slight North to South gradient in the rate of positivity. In Houston, among 250 donors, the rate of positivity was 2.8%, with 4.23% of donors over 30 being positive. In this group, recipients were surveyed and none were documented to have seroconverted. Two recipients experienced post transfusion perturbations in HTLV-I reactivity. On careful analysis utilizing alternate technical approaches, these suspect seroconverters proved to be false positive due to B-cell alloantigen reactivity possibly linked to the pregnancy-related complications for which they were transfused. In Kingston, Jamaica, among 450 donors, 4.8% were positive.

Immunogenetics of HTLV-I:

In a previous study, HLA typing of virus-positive ATL cell lines revealed the presence of more than the expected number of HLA-A and B antigens, particularly antigens of the HLA B-5 cross-reactive group. During the current year, this observation was followed up by evaluating cord blood cells infected by cocultivation in vitro. Reactivity was detected on these cells with a monoclonal antibody, 4D12, which detects an epitope of the B5 cross-reactive antigen series as well as with human heteroantisera. Expression of

4D12 correlates with the presence of HTLV-I in that it is detectable in virus-positive but not virus-negative cell lines, and more recently in hamster-human hybrids where the 4D12 expression correlated with the presence of integrated virus and not the presence or absence of the HLA chromosome 6 in the hybrid cell line. These findings raise the possibility that persons expressing antigens of the B5 group may have increased susceptibility to virus infection and/or development of disease. Population-based immunogenetic studies are being planned as part of efforts in Jamaica to systematically explore this hypothesis. These and related immunologic studies provide a model for evaluating possible etiologic mechanisms of lymphoid malignancy or diseases of altered immunity. B-cell lines infected by HTLV-I were cultured from two ATL patients. 4D12 expression and anti-TAC antibodies were detected on the cell surface of these virus-positive B-cell lines. The expression of surface immunoglobulins represented a terminally differentiated phenotype resistant to further growth. However, less mature B-cells from the culture grew and expressed this phenotype in approximately 1/3 of cells. The data suggest that B- as well as T-cells are infectable with HTLV and that the expression of extra HLA reactivity is limited to the virus-infected cell.

Cytogenetic Studies of HTLV-I Positive Malignancies:

Cytogenetic analysis of tumor tissue from cases of HTLV-I associated ATL both in the United States and in Jamaica, done in collaboration with Dr. Rowley in Chicago and Dr. Whang-Peng at the NIH, have shown the presence of chromosomal abnormalities in the great majority of cases, although (as is similar to the reports from Japan) no common chromosomal abnormality is seen in every case. Cytogenetic studies of cell lines established from those patients in comparison to the fresh tumor tissue, done in collaboration with Dr. Nowell in Philadelphia, showed that while the fresh tumor tissue almost always had chromosomal abnormalities, the cell lines were usually chromosomally normal. This may have implications concerning the possible relationship of the above described chromosomal abnormalities and the initial events of transformation by HTLV-I. Future efforts will focus on identifying tumor cells with specific translocations for molecular studies of T-cell receptor rearrangements and other molecular genetic analyses.

HTLV Computer Data Base:

Section personnel have implemented comprehensive computer-based systems in support of this and the HTLV-III project. The existing Family Studies computer system was readily adapted to HTLV studies, even though the HTLV project is considerably more complex. Thus, we are now able to link existing clinical information to the biologic specimens. The inventory management system retains the ability to track individual specimens, and now incorporates features designed to facilitate receipt and handling of larger batches of serum. During the last year, over 70,000 samples were received, disbursed, and tested. Data from several assays have been transferred from the laboratory through direct computer links, and statistical evaluation of their sensitivity, specificity, and reproducibility are being performed and monitored in conjunction with Biostatistics Branch statisticians. In

addition, a system for data entry, editing, and analysis has been established for use with the IBM PC and is presently being utilized in Jamaica and Panama.

The Section has modified the automated HTLV-I data-base and biospecimen repository systems to accommodate the special requirements for AIDS/HTLV-III research, providing the ability to efficiently track specimens, evaluate new data and preserve patient confidentiality.

PROJECT 2: ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) AND HTLV-III

AIDS is an outbreak of highly lethal opportunistic infections and Kaposi's sarcoma that first appeared in homosexual men in New York City and California in 1979. Since that time more than 10,000 AIDS cases have been diagnosed, and the number of cases has doubled in each subsequent 6-12 month period. In addition, AIDS has been identified in other groups, including drug addicts, Haitians, hemophiliacs and transfusion recipients, heterosexual partners and children of risk group members and in areas of tropical Africa.

The Section approach of interdisciplinary clinical and laboratory studies in high-risk groups was applied in order to assess risk factors affecting both the overt outcome and the subclinical immunologic changes that antedate clinical disease. The Section had in place both the epidemiologic resources and the sophisticated immunologic laboratory required to study AIDS at the national and international level when this urgent medical problem became manifest.

Our overall strategy has been to identify the risk factors related to the occurrence of AIDS; to develop a repository of information and biological specimens for testing hypotheses regarding the etiology, early detection and prevention of AIDS; and to examine these hypotheses with relevant clinical, epidemiologic, and laboratory tools by coordinating diverse resources available at NIH and elsewhere.

Rather than attempt to duplicate efforts already under way regionally in a number of university and medical centers, or to undertake the case-finding role that is the province of the Centers for Disease Control, the Section has applied strategies traditional for EEB studies. We selected study locations to permit comparisons between high,intermediate, and low risk areas, and to keep survey design and laboratory test procedures as comparable as possible. In addition, provisions for follow-up have been implemented to study the natural history and outcome of the study cohorts, as defined by various exposure measures. This approach produced a unique resource of banked biological specimens on persons in different risk groups, in different localities, and at different times in the course of the outbreak.

In May 1984, the isolation and characterization of the third member of the human T-cell lymphotropic virus family was reported. The Section, because of a longstanding collaboration, worked closely with Dr. Robert C. Gallo and the

Laboratory of Tumor Cell Biology (LTCB) (Project No. Z01-CM-7150-01), to further assess the relationship between HTLV-III and AIDS. Sera from various groups from our repository with diverse clinical and subclinical immunodeficiency and AIDS and related conditions were tested and found to be positive in substantial numbers, while historical population-based sera from a low-risk AIDS region and sera from AIDS low-risk foreign countries were negative. These data were analyzed in an assessment of test performance characteristics and a seminal paper published by our group documented the high sensitivity and specificity of the first generation HTLV-III antibody test. These data and a substantial time commitment by Section staff were instrumental in moving forward the Department of Health and Human Services' objectives for the implementation of a reliable blood bank screening assay. In this regard, Section staff played a major role in developing PHS guidelines for protecting the nation's blood supply by implementation of the HTLV-III antibody screening assay. In addition, we helped develop guidelines concerning recommendations for use, interpretation, and the understanding of clinical implications of seropositivity as determined from natural history studies conducted by our group (see below).

AIDS and Cancer:

A central question of interest to NCI is the relationship between AIDS and malignancies. While the relationship between AIDS and Kaposi's sarcoma is well established, other malignancies, particularly the non-Hodgkin's lymphomas, have also been reported to occur in the AIDS-risk groups. To examine these relationships on a statistically sound basis, we have used the NCI Surveillance, Epidemiology and End Results (SEER) Program to undertake studies of cancer incidence among never married young men. Results available through 1982 document an enormous increase in Kaposi's sarcoma in the AIDS high-risk areas while the magnitude of changes for other malignancies in SEER areas is small or absent. These data argue that some of the antedotal reports of AIDS-associated malignancies may be spurious or that additional person-years-at-risk will need to be accumulated to detect significant trends. Other than Kaposi's sarcoma, Burkitt's-like tumors were the only tumors occurring at a significant excess, and even this was only marginally more common than expected. As an outgrowth of this work, a sophisticated computerized system has been developed to allow for continued monitoring to define and quantify the emergence of cancer trends in sentinal populations followable through the SEER registries. Thus, as new antedotal leads are reported, an epidemiologically quantifiable system is in place to verify and track the impact of these emerging cancers in relationship to AIDS.

Cohort Studies of Healthy Populations at Risk of AIDS

Within months of the first reported cases of AIDS in the spring of 1981, Section staff developed a series of prospectively defined cohorts among healthy at-risk study subjects. These cohorts were established to provide a base for accessing risk factors and outcomes associated with the putative etiologic agent of AIDS. With the discovery of HTLV-III, this bank of biologic samples and epidemiologic data have served as a key resource for

proving the etiologic link of HTLV-III to AIDS; the nature of the spectrum of HTLV-III related outcomes; and the natural history of virus infection and risk for AIDS among seropositives.

Danish Homosexual Cohort: In November 1981, 259 homosexual men in Denmark were interviewed. In March 1982, a cohort of 80 men classified as cases (based on nitrite use or travel to the U.S.) or matched controls who lacked these exposures, were recontacted and phlebotomized. The longitudinal study of this cohort has continued, with follow-up interview and clinical data and laboratory specimens collected in an ongoing fashion at yearly intervals. Analysis of HTLV-III serology in this cohort documented that the seroprevalence of HTLV-III antibody positivity was 9% in the Danish cohort in 1981, and that seronegative cohort members have seroconverted at a rate of approximately 1% per month. The major risk factor for seropositivity among cohort members was contact with homosexuals from the U.S. suggesting secondary spread of the agent from the U.S. to Denmark. A large number of homosexual partners and anal receptive intercourse are additional risk factors for seropositivity. Clinical AIDS developed in 9% of the seropositive cohort over a 32 month period. Lesser clinical manifestations of immunodeficiency were also detected in 20% of seropositives. In one cohort member, a decline in antibody titer was a preclinical harbinger of AIDS suggesting that antibody titers may have prospective significance.

New York and Washington, D.C. Male Homosexual Cohorts: Cohorts of healthy homosexuals from New York and Washington, D.C. numbering 250 men have been characterized clinically, demographically, and immunologically and followed prospectively at yearly intervals. Detailed analyses showed that (a) low helper T-cell counts were more common in New York; (b) low helper T-cell counts apparently could be "acquired" by Washington, D.C., men through homosexual contacts in AIDS endemic areas; and (c) low helper T-cell counts were closely associated with receptive anal intercourse. The observations are directly attributable to HTLV-III indicating that altered T-cell subsets are one manifestation of immunoablative retroviral infections. In addition, studies of these cohorts document that HTLV-III infection is significantly more common in frank AIDS, in "lesser AIDS," and in the lymphadenopathy syndrome than in unaffected homosexual men and that HTLV-III infection is strongly correlated to suppressed T-cell subsets. HTLV-III exposure, thus, serves to provide a unifying framework for defining the spectrum of AIDS-related immunodeficiency states.

Prospective follow-up of these cohorts has documented that 12% of the HTLV-III positive men in the Washington cohort and 20% of the HTLV-III positive men in the New York cohort have developed clinical AIDS while an additional 15% to 30% have developed lesser manifestations of AIDS.

Taken as a whole, the data from this cohort strongly argue that HTLV-III is the underlying etiologic agent of AIDS; a conclusion supported by the observed seroconversion and subsequent development of AIDS in study group members and the observation that AIDS only develops in seropositive study subjects.

Studies on Hemophiliacs: In late 1982, a cohort of 50 hemophiliac patients, two of whom had AIDS, was evaluated immunologically with compilation of their lifetime exposure to concentrated plasma clotting factors. Depressed helper/suppressor ratios were observed in 20%, and preliminary analysis demonstrated a correlation between the number of clotting factor transfusions and low ratios. This suggests a dose-response relationship to a blood-borne pathogen in the etiology of the immune dysfunction in hemophiliacs. Subsequently, we have documented for the first time that HTLV-III infection is most closely related to Factor VIII concentrate therapy, with over 70% of such patients being antibody positive. This risk is much less prominent in those with Factor IX deficiency, a finding which correlates with the much less frequent occurrence of AIDS in that clinical group. Using stored serum samples from cohort members dating back to the mid 1970s, we have demonstrated that the earliest HTLV-III seroconversion occurred in 1979 and that the majority of hemophiliacs seroconverted during 1981 and 1982. Among 10 pre-1981 seroconverters, all have either generalized lymphadenopathy and/or subclinical immunologic perturbations, while those seroconverting after 1981 had such abnormalities in 20%. These data emphasize the concept that HTLV-III infection is an ongoing immunoablative process with a long latent period to clinically detectable outcome.

Studies undertaken among European hemophiliacs have found similiar results. Prevalence of seropositivity was about as high as in the U.S. hemophiliac population among those using commercial factor VIII concentrate preparation (which is made from U.S. sources). The virus appeared to be introduced into European hemophiliacs about 1980. We have demonstrated spread from 1 male hemophiliac to a female sex partner, possibly related to anal sexual intercourse.

Preliminary results from HTLV-III culture and serologic studies of the wives of hemophiliacs suggest that antibody-negative HTLV-III infection may be both highly prevalent (at least 10%) and persistent for years in these women. Attempts to evaluate the HTLV-III culture methods for sensitivity and specificity and to reproduce and expand these findings in other populations (household contacts, laboratory workers) are in progress.

Parenteral Drug Users: The Family Studies Section has signed a Memorandum of Understanding with the National Institute on Drug Abuse (NIDA) detailing collaborative efforts on the drug user risk group. A questionnaire emphasizing the ascertainment of detailed drug use histories was developed and tested. Collaborations with investigators in regions of high and low AIDS prevalence have been established. The Section has been issued a Certificate of Confidentiality from NIDA for its AIDS studies, providing our study subjects with the most rigorous legal protection available for research on sensitive data about illegal activities.

In 1982, 35 parenteral drug users from a methadone detoxification program and 35 parenteral drug users hospitalized for soft-tissue infections in New York were characterzied immunologically and clinically. Analysis of sera from 1982 indicates significant serologic reactivity for antibodies to HTLV-I, -II, and

-III. The HTLV-III seropositivity rate was strongly associated with and consistent with the tendency to share needles with persons of the same race in this rather segregated community. The rates of HTLV-I and-II seropositivity, while controlling for race and HTLV-III status, were higher in the soft tissue infection group compared to the detoxification group, suggesting a possible role for HTLV-I and -II in the development of immune deficiency states. Our Section is now engaged in following these study participants as part of a longitudinal cohort study. One HTLV-III seropositive detoxification program individual is known to have died of AIDS, and another seropositive died of interstitual pneumonitis, presumably AIDS related.

Whereas 29% of AIDS cases nationally have a history of parenteral drug use, 53% have such a history in New Jersey. The case distribution is geographically clustered about a Jersey City/Newark/New York City epicenter. The Family Studies Section designed and completed a seroepidemiologic study of nearly 1,000 parenteral drug users in New Jersey to examine risk factors for HTLV-III exposure, in collaboration with NIDA and the New Jersey State Department of Health (NJSDH). Preliminary analyses indicate 1) a parallel between HTLV-III and AIDS distribution, further strengthening the association; 2) that more frequent parenteral drug use in the preceding year was significantly associated with a higher rate of HTLV-III seropositivity; and 3) that female drug users were at least as likely as males to be seropositive. The cohort will be prospectively evaluated for the development of AIDS, including periodic follow-up with the drug programs involved, as well as matching by NJSHD against their AIDS registry.

Investigation of the spouses of index subjects will constitute a separate but related study designed to explore risk factors for heterosexual transmission of HTLV-III. Maternal/infant transmission will also be investigated as part of planned collaborative studies involving predominantly IV drug using populations at the State University of New York, Downstate Medical Center, in collaboration with investigators for the National Institute of Child Health and Human Development.

Comparative Cohort Studies:

The five established cohorts (homosexual men in Denmark, New York, and Washington, hemophiliacs, and drug users) have been evaluated for the development of AIDS and related conditions. The cumulative incidence of AIDS was 11% among HTLV-III seropositive individuals within 32 months of follow-up and ranged from 4% in the drug users to 20% in the New York homosexual men. The latter group had a significantly higher cumulative incidence of AIDS than the other groups combined (4-12%). The reasons for this higher rate could include cofactors (5 cases of Kaposi's sarcoma in New York homosexual men vs. none in the other cohorts) and/or longer time at risk, particularly since New York homosexual men are at one of the original epicenters of AIDS in the U.S.

Health Care Worker Studies:

The Family Studies Section is conducting a serologic assessment of HTLV-I

exposure among LTCB and FSS workers in an ongoing fashion. With the discovery of HTLV-III, testing for this agent as well is being undertaken. No worker was positive for HTLV-III antibodies. One person from an HTLV-I endemic region was positive for HTLV-I, but on banked sera, this positivity antedated research studies of retroviruses by the laboratory where she worked. Prospective follow-up with extensive provisions for the protection of confidentiality and privacy of study subjects are in progress.

Downstate Medical Center, Brooklyn, New York, is a large city hospital with extremely intensive exposure of workers to AIDS patients (over 300 hospitalized in the last 3 years) as well as seropositive risk group members. In the summer of 1984, a collaborative effort to assess risk of retroviral infection was begun. Preliminary data confirm the finding of a low risk of transmission of HTLV-III in the patient care setting.

International Studies

AIDS is an emerging international problem and, as outlined above, one of the earliest cohorts assembled was developed in Denmark. Section staff have been instrumental in discerning international patterns of AIDS spread and, in particular, the link of AIDS in some African populations.

Studies in Africa: The focus of our studies in Africa has been HTLV-III seroepidemiology in normal populations of Kenya and Zaire. We have demonstrated a surprisingly high prevalence of ELISA seropositivity for HTLV-I, HTLV-II, and HTLV-III among healthy subjects. There is marked regional variations that corresponds to malaria incidence. We are currently exploring the specificity of the observed reactions in the ELISA and other tests for retroviruses. We have also investigated the biology of African Kaposi's sarcoma. There is no evidence of either HTLV-III involvement or immunosuppression underlying the occurrence of the endemic form. Data elsewhere suggest, however, that HTLV-III and associated immunodeficiency may be involved in the aggressive form of Kaposi's sarcoma emerging in some populations. Our studies indicate no role for either cytomegalovirus (CMV) or Epstein-Barr virus (EBV) in endemic Kaposi's sarcoma. Studies to determine the clonality of endemic Kaposi's sarcoma are underway utilizing molecular genetic approaches on materials collected in cases as part of ongoing research field studies.

Studies on Haitians

In the summer and fall of 1984, the Family Studies Section in conjunction with Dr. Sheldon Landesman and colleagues of the Downstate Medical Center in Brooklyn, New York, assessed the role of HTLV-III exposure in Haitians with AIDS and also among Haitian immigrant controls who came to health fairs in New York City. All the Haitian AIDS cases had HTLV-III antibodies strengthening the association of this virus with AIDS. None of the controls from the normal Haitian population had evidence of HTLV-III antibody, in contrast to seropositivity rates in excess of 50% for parenteral drug users

and homosexual men in New York City. Based in part on results of these studies, PHS officials removed Haitians from AIDS risk group classification.

EEB has also been actively involved in a collaborative study of HTLV-III and AIDS in conjunction with an NIH grantee, Dr. Warren Johnson of Cornell Medical School. Results of a case-control study of AIDS cases, their family members' and friends' risk factors for positivity in addition to bisexuality include promiscuous heterosexual contact, blood transfusion, needle exposure and perinatal exposure. Current studies are aimed at evaluating interaction among the various risk factor parameters in an attempt to quantify the level of risk associated with these factors.

Trinidad and Jamaica:

Because of our ongoing studies with the University of West Indies campuses in Trinidad and Jamaica, we have been asked to assist in the evaluation of HTLV-III infection in these HTLV-I endemic areas. Unlike HTLV-I which appears to be a longstanding and widespread virus in these areas, HTLV-III is newly introduced, with seropositivity and clinical AIDS confined so far to known risk group members. As in other low rate areas, the major risk factor for seropositivity appears to result from homosexual contact with persons from AIDS areas.

Immunogenetic Marker of AIDS

Follow-up on evidence that HLA type DR5 may be a risk factor for Kaposi's sarcoma, we have performed HLA typing on NIH Clinical Center AIDS patients. Preliminary analysis shows that DR5 is excessive not only in Kaposi's sarcoma but also in other AIDS patients. Moreover, the newly recognized HLA specificity MB2 appears to be even more closely associated with AIDS than is DR5.

Non-HTLV Virus Studies:

Epstein Barr Virus (EBV) and Cytomegalovirus (CMV) Studies

As part of AIDS-related studies, the relationship between HTLV-III infection and EBV and CMV has been investigated; so far, no effect has been seen.

In addition, we have undertaken studies on the biology of Kaposi's sarcoma in Africa with a particular focus on the possible role of CMV. No differences in antibody status or in integrated genomic CMV have been found to date but additional studies are in progress.

As part of ongoing studies on Burkitt's lymphoma, a tumor associated with the EBV, we have extended the HLA typing studies on cases and controls in Ghana and continue to observe the earlier reported excess of DR7 in cases.

In a study comparing the incidence of hepatoma with the prevalence of hepatitis in both Greenland and Denmark, we were able to confirm that

Greenland is an area of high hepatitis infection and high carrier rates. Despite this, and in conflict with the hypotheses relating hepatitis and hepatoma, we found no excess of hepatoma in the Greenland population.

Significance to Biomedical Research and the Program of the Institute:

The discovery of the first human leukemia virus and the pioneering studies by Section personnel documenting the relationship worldwide to certain forms of lymphoid malignancies provides the first direct evidence that an exogenous retrovirus is etiologically linked to human cancer. Studies of this virus and its relationship to human disease provide a model system for investigating direct and indirect mechanisms of human carcinogenesis using easily quantifiable measures of virus exposure and powerful tools of molecular biology. The fact that a minority of exposed persons develop cancer provides an opportunity for dissecting modifying factors in the malignancy process using epidemioloic techniques. The recent discovery that a member of this retrovirus family, HTLV-III, also has immunosuppressive potential as the putatives in family, HTLV-III, also has immunosuppressive potential as the putative etiologic agent of AIDS has clear public health implications. Furthermore, the mechanism(s) by which this agent predisposes to cancer provides a clear opportunity for precisely quantifying the role of immunosuppression in cancer risk, as well as exploring the etiologic relationship of HTLV-III to Kaposi's sarcoma. Thus, the emerging family of retroviruses provides a rich resource for understanding models of human cancer etiology.

Proposed Course:

The Family Studies Section has experienced a realignment in scientific and administrative structure aimed at maintaining a strong program area in host factor studies and developing an organized and comprehensive program focusing on the rapidly changing field of retrovirus epidemiology. In the near future, further development of new resources to support these areas will be implemented through targeted staffing efforts and development of support contracts. The application of in-depth multidisciplinary approaches to cancer etiology studies will continue to be the underlying philosophy applied to Section activities in all program areas. Thus, the experience and expertise of senior staff will be utilized across program areas particularly in providing scientific consultation.

Studies of HTLV-I have primarily focused on hypothesis-generating and descriptive studies that have led to the formulation of testable hypotheses. Thus, although there will continue to be a major focus on descriptive studies aimed at further quantifying the distribution of the virus, this effort will be bolstered by newly developed contract resources to systematically target such efforts with more in-depth information collection. In addition, a large number of recently defined available serum collections will be selectively surveyed for informative samples for testing. A number of analytic studies are recently underway or planned as well. Through research contracts in the viral endemic areas of Jamaica, Trinidad, and Panama, a case-control study of

HTLV-I infection in relation to lymphoid malignancy has been implemented and is in the second year of case recruitment. This three-year study will attempt to define parameters relevant to the carcinogenesis process as well as attempt to understand circumstances of viral infection through a questionnaire interview and multidisciplinary laboratory study. In parallel with this are population-based studies in these HTLV-I endemic areas aimed at investigating factors associated with viral infection. In addition, other analytic efforts will focus on investigation of unique migrant populations from high- to low-rate viral areas under a research contract with Kuakini Medical Center in Hawaii and the University of Hawaii campus in Okinawa.

AIDS studies have been reoriented to focus on better understanding the relationship of HTLV-III exposure in the disease process. Previously planned analytic studies of various high risk groups, particularly parenteral drug users, and selected homosexual cohorts, have been restructured to take advantage of this new discovery. The major focus of such studies will be aimed at defining the natural history of the virus and its end points and the cofactors that predispose to various outcomes. A particular emphasis will be on the relationship of this exposure to malignancy, particularly Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma.

An analytic study of T-cell subsets, a marker previously associated with AIDS and more recently to HTLV-III exposure, will be completed in a population-based sampling of normal Washington, D.C. residents to better quantify other cofactors of this outcome. The opportunity to characterize the distribution of various types of HTLV, particularly HTLV-III in African populations at risk for Kaposi's sarcoma and AIDS, will be explored as a method for understanding the natural pattern of infections and interactions of various viral subtypes in populations sharing multiple exposures to various retrovirus types. This should aid particularly in helping to understand the natural history of retroviruses in relationship to disease.

Publications:

Bartholomew, C., Charles, W., Saxinger, C., Blattner, W., Robert-Guroff, M., Raju, C., Ratan, P., Ince, W., Quamina, D., Basdeo-Maharaj, K. and Gallo, R. C.: Racial and other characteristics of human T-cell leukaemia/lymphoma (HTLV-I) and AIDS (HTLV-III) in Trinidad. Br. Med. J. 290: 1243, 1985.

Biggar, R. J., Ebbesen, P., Melbye, M., Mann, D. L., Goedert, J. J., Weinstock, R., Strong, D. M. and Blattner, W. A.: Low T-lymphocyte ratios in Danish homosexual men, epidemiologic evidence for a transmissible agent. JAMA 251: 1441-1446, 1984.

Biggar, R. J., Gigase, P. L., Melbye, M., Kestens, L., Sarin, P., Bo A. J., Alexander, S., Collins, W. C., Paluko, L., deFeyter, M. and Blattner, W. A.: HTLV retrovirus antibodies associated with malaria in Africa. Lancet (In Press).

Biggar, R. J., Horm, J., Fraumeni, J. F., Jr., Greene, M. H. and Goedert, J. J.: The incidence of Kaposi's sarcoma and mycosis fungoides in the United States and Puerto Rico, 1973-81. J. Natl. Cancer Inst. 73: 89-94, 1984.

Biggar, R. J., Horm, J., Lubin, J. H., Goedert, J. J., Greene, M. H. and Fraumeni, J. F., Jr.: Cancer trends in a population at risk of Aquired Immunodeficiency Syndrome. J. Natl. Cancer Inst. 74: 793-797, 1985.

Biggar, R. J., Johnson, B. K., Oster, C., Sarin, P. S., Ocheng, D., Tukei, P., Nsanze, H., Alexander, S., Bodner A. J., Siongok, T., Gallo, R. C. and Blattner, W. A.: Regional variation in prevalence of antibody against human T-lymphotropic virus types I and III in Kenya, East Africa. Int. J. of Cancer (In Press).

Biggar, R. J., Melbye, M., Ebbesen, P., Alexander, S., Nielsen, J. D., Sarin, P., Faber, V.: HTLV-III antibody variation in AIDS and AIDS-risk homosexual men: Decline prior to onset of AIDS-related illness. JAMA (In Press).

Biggar, R. J., Melbye, M., Kestens, L., deFeyter, M., Saxinger, C., Bodner, A. J., Blattner, W. A. and Gigase, P.L.: Seroepidemiology of HTLV-III antibodies in a remote population of eastern Zaire. Brit. Med. J. 290: 808-810, 1985.

Biggar, R. J., Melbye, M., Kestens, L., Sarngadharan, M. G., deFeyter, M., Blattner, W. A., Gallo, R. C. and Gigase, P. L.: Kaposi's sarcoma in Zaire is not associated with HTLV-III infection. N. England J. Med. 311: 1051-1052, 1984.

Biggar, R. J., Pandey, J. P., Henle, W., Nkrumah, F. K. and Levine, P. H.: Humoral immune response to Epstein-Barr virus antigens and immunoglobulin allotypes in African Burkitt's lymphoma patients. Int. J. Cancer 33: 577-580, 1984.

Biggar, R. J., Saxinger, C., Gardiner, C., Collins, W. E., Levine, P. H., Clark, J. W., Nkrumah, F. K., Gallo, R. C. and Blattner, W. A.: Type-I HTLV antibody in urban and rural Ghana, West Africa. Int. J. Cancer 34: 215-219, 1984.

Blattner, W. A.: Human retroviruses. In Feigin, R. D. and Cherry, J. D. (Eds.): Textbook of Pediatric Infectious Diseases, Philadelphia, Saunders (In press).

Blattner, W. A., Biggar, R. J., Weiss, S. H., Melbye, M. and Goedert, J. J.: Perspective on AIDS from epidemiologic studies of HTLV-III. Ann. Int. Med. (In Press).

Blattner, W. A., Biggar, R. J., Weiss, S. H., Clark, J. W. and Goedert, J. J.: The epidemiology of human lymphotrophic retroviruses: overview. Cancer Res. (In Press).

Blattner, W. A., Clark, J. W., Gibbs, W. N., Williams, C. K. O., Nomura, A., Mann, D., Saxinger, C., Robert-Guroff, M. and Gallo, R. C.: HTLV: Epidemiology and relationship to disease. In Miwa, M., et al. (Eds.): Proceedings 15th International Symposium of the Princess Takamatsu Cancer Research Fund, Japan, Sci. Soc. Press, Tokyo, VNU, Science Press, Utrecht, (In Press).

Blattner, W. A., Clark, J. W., Gibbs, W. N., Jaffe, E. S., Robert-Guroff, M., Saxinger, W. C. and Gallo, R. C.: HTLV: Epidemiology and relationship to human malignancy. In Gallo, R. C., Essex, M. E. and Gross, L. (Eds.): Cancer Cells: Human T-cell Leukemia/Lymphoma Viruses. New York, Cold Spring Harbor Laboratory, 1984, Chapter 3, pp. 267-274.

Blattner, W. A. and Gallo, R. C.: Epidemiology of human retroviruses. Leuk. Res. 9: 697-698, 1985.

Blattner, W. A., Nomura, A., Clark, J. W., Ho, G. F. Y., Nakao, Y., Gallo, R., and Robert-Guroff, M.: HTLV-I in Japanese migrant populations in Hawaii. N. Engl. J. Med. (In Press).

Blattner, W. A. and Hoover, R. N.: Cancer in the immunosuppressed host. In DeVita, V. T., Hellman, S. and Rosenberg, S. A. (Eds.): Cancer: Principles and Practice of Oncology, Philadelphia, Lippincott, 1985, pp. 1999-2006.

Blattner, W. A., Robert-Guroff, M., Kalyanaraman, V. S., Sarin, P., Jaffe, E. S., Blayney, D. W., Zener, K. A. and Gallo, R. C.: Preliminary epidemiologic observations on a virus associated with T-cell neoplasia in man. In Magrath, I. T., O'Conor, G. T. and Ramot, B. (Eds.): Pathogenesis of Leukemias and Lymphomas: Environmental Influences. New York, Raven Press, 1984, Vol. 27, pp. 339-348.

Blattner, W. A., Saxinger, C. W. and Gallo, R. C.: HTLV-I, the prototype human retrovirus: epidemiologic features. In Dodd, R. Y. and Barker, L. S. (Eds.): Infection Immunity and Blood Transfusion, New York, Alan R. Liss, 1985, pp. 223-244.

Blayney, D. W., Saxinger, W. C., Hollinger, F. B., Postal, M. G., Gallo, R. C., and Blattner, W. A.: Transfusion with donor blood containing HTLV-I antibodies. Blood (In Press).

Broder, S., Bunn, P. A., Jaffe, E. S., Blattner, W. A., Gallo, R. C., Wong-Staal, F., Waldmann, T. A. and DeVita, V. T.: T-cell lymphoproliferative syndrome associated with human T-cell leukemia/lymphoma virus. Ann. Intern. Med. 100: 543-557, 1984.

Clark, J. W., Blattner, W. A. and Gallo, R. C.: HTLV: Epidemiology and disease relationship. In Aoki, T., Tsubura, E. and Urushizaki, I. (Eds.): Manipulation of Host Defense Mechanisms. Tokyo, Excerpta Medica, 1984, pp. 124-136.

Clark, J. W., Blattner, W. A. and Gallo, R. C.: Human T-cell leukemia viruses and T-cell lymphoid malignancies. In Petersdorf, R. Q., Adams, R. D., Braunwald, E., Isselbacher, K. J., Martin, J. B. and Wilson, J. D. (Eds.): Harrison's Update of Internal Medicine, Vol. VIII, New York, McGraw-Hill Company (In Press).

Clark, J. W., Hahn, B. H., Mann, D. L., Wong-Staal, F., Popovic, M., Richardson, E., Strong, D. M., Lofters, W. S., Blatner, W. A., Gibbs, W. N., and Gallo, R. C.: Molecular and immunologic analysis of an HTLV positive CLL case from Jamaica. Cancer (In Press).

Clark, J. W., Robert-Guroff, M., Ikehara, O., Henzan, E. and Blattner, W. A.: The human T-cell leukemia/lymphoma virus type-I (HTLV-I) in Okinawa. Cancer Res. (In Press).

Dobozin, B. S., Judson, F. N., Cohn, D. L., Penley, K. A., Rickmann, P. E., Blaser, M. J., Sarin, P. S., Weiss, S. H. and Kirkpatrick, C. H.: The relationship of abnormalities of cellular immunity to antibodies to HTLV-III in homosexual men. Ann. Intern. Med. (In Press).

Ebbesen, P., Melbye, M. and Biggar, R. J.: Quantitative data on lifestyle factors of young Danish homosexuals. Antibiot. Chemother. 32: 112-116, 1984.

Ebbesen, P., Melbye, M. and Biggar, R. J.: Sex habits, recent disease and drug use in two groups of Danish male homosexuals. Arch. Sex. Behav. 3: 291-300, 1984.

Ebbesen, P., Melbye, M. and Biggar, R. J.: AIDS and cancer. In Wolff, J. P. and Cott, J. S. (Eds.): Proc. of the 2nd Annual ECP Symposium on Hormones and Sexual Factors in Human Cancer Aetiology. New York, Elsevier Science Publishers, 1984, pp. 115-122.

Ebbesen, P., Melbye, M. and Biggar, R. J.: AIDS in Europe. Acquired Immune Deficiency Syndrome. New York, Alan R. Liss, Inc., 1984, pp. 3-7.

Eyster, M. E., Goedert, J. J., Sarngadharan, M. G., Weiss, S. H., Gallo, R. C., and Blattner, W. A.: Development and early natural history of HTLV-III antibodies in persons with hemophilia. JAMA 253: 2219-2223, 1985.

Frank, E., Weiss, S. H., Compas, J. C., Beinstock, J., Weber, J., Bodner, A., Landesman, S. H.: AIDS in Haitian-Americans: A reassessment. Cancer Res. (In Press).

Gallo, R. C. and Blattner, W. A.: Human T-cell leukemia/lymphoma viruses: ATL and AIDS. In DeVita, V. T., Helman, S. and Rosenberg, S. S. (Eds.): Important Advances in Oncology. New York, J. P. Lippincott Co., 1985, pp. 104-138.

Gallo, R. C., Sarin, P. S., Blattner, W. A., Wong-Staal, F. and Popovic, M.: T-cell malignancies and human T-cell leukemia virus. Semin. Oncology 11: 12-17, 1984.

Gallo, R. C., Wong-Staal, F., Clarke, M. F., Guo, H-G, Westin, E., Saxinger, W. C., Blattner, W. A. and Reitz, M. S.: Human T-cell leukemia viruses and oncogenes and the origin of some human leukemias and lymphomas. In Zarda, L. (Ed.): Proceedings of the First Intl. Conf. on Cancer Res. New York, Academic Press, Inc., 1985, pp. 85-100.

Gardiner, C., Biggar, R. J., Collins, W. E. and Nkrumah, F. K.: Malaria in urban and rural areas of southern Ghana: A survey of parasitaemia antibodies, and antimalarial practices. Bull. WHO: 62: 607-613, 1984.

Gibbs, W. N., Lofters, W. S., Campbell, M., Hanchard, B., LaGrenade, L., Cranston, B., Hendricks, J., Jaffe, E., Saxinger, C., Robert-Guroff, M., Gallo, R. C., Clark, J. and Blattner, W. A.: Non-Hodgkin's lymphoma in Jamaica and its relationship to adult T-cell leukemia. Ann. Int. Med. (In Press).

Gibbs, W. N., Lofters, W. S., Campbell, M., Hanchard, B., LaGrenade, L., Clark, J., Cranston, B., Saxinger, C., Franchini, G., Gallo, R.C. and Blattner, W. A.: Adult T-cell leukemia/lymphoma (ATL) in Jamaica and its relationship to human T-cell leukemia/lymphoma virus type I (HTLV)-associated lymphoproliferative disease. In Miwa, M., et al. (Eds.): Retroviruses in Human Lymphoma/Leukemia, Japan Sci. Soc. Press, UNV Science Press, Utrecht, 1985.

Ginzberg, H. M. and Weiss, S. H.: Blood counts in male parenteral drug users. JAMA 253: 514, 1985.

Goedert, J. J.: Recreational drugs: Relationship to AIDS. In Selikoff, I. G., Teirstein, A. S. and Hirschman, S. Z. (Eds.): Acquired Immune Deficiency Syndrome, New York, Academic Press, Inc., 1985, pp. 192-199.

Goedert, J. J., Biggar, R. J., Winn, D. M., Mann, D. L., Strong, D. M., DiGioia, R. A., Grossman, R. J., Sanchez, W. C., Kase, R. G., Greene, M. H., Byar, D. P., Hoover, R. N., and Blattner, W. A.: Decreased helper T lymhocytes in homosexual men: I. Sexual contract with high-incidence areas for the acquired immunodeficiency syndrome. Am. J. Epidemiol. 121: 629-636, 1985.

Goedert, J. J., Biggar, R. J., Winn, D. M., Mann, D. L., Strong, D. M., DiGioia, R. A., Grossman, R. J., Sanchez, W.C., Kase, R. G., Greene, M. H., Byar, D. P., Hoover, R. N. and Blattner, W. A.: Decreased helper T lymphocytes in homosexual men: II. Sexual practices. Am. J. Epidemiol. 121: 637-644, 1985.

Goedert, J. J. and Blattner, W. A.: The epidemiology of the acquired immunodeficiency syndrome. In DeVita, V. T., Hellman, S. and Rosenberg, S. A.

(Eds.): AIDS: Etiology, Diagnosis, Treatment, and Prevention. Philadelphia, Lippincott, 1985, pp. 1-30.

Goedert, J. J., Biggar, R. J., Winn, D. M., Mann, D. L., Strong, D. M., DiGioia, R. A., Grossman, R. J., Sanchez, W. C., Kase, R. G., Greene, M. H., Byar, D. P., Hoover, R. N., and Blattner, W. A.: Decreased helper T lymphocytes in homosexual men: I. Sexual contact with high-incidence areas for the acquired immunodeficiency syndrome. Am. J. Epidemiol. 121: 629-636, 1985.

Goedert, J. J., Eyster, M., Salahuddin, S. Z., Sarngadharan, M. G., Bodner, A. J., Markham, P. D., Neuland, C. Y., Melbye, M., Weiss, S. H., Clark, J. W., Biggar, R. J., Gallo, R. C., Blattner, W. A., and Sarin, P. S.: Prolonged HTLV-III carrier state in seronegative wives of hemophiliacs. Lancet (In Press).

Goedert, J. J. and Gallo, R. C.: Epidemiological evidence that HTLV-III is the AIDS agent, European J. Epidemiol. (In Press).

Goedert, J. J., Sarngadharan, M. G., Biggar, R. J., Weiss, S. H., Winn, D. M., Grossman, R. J., Greene, M. H., Bodner, A. J., Mann, D. L., Strong, D. M., Gallo, R. C. and Blattner, W. A.: Determinants of retrovirus (HTLV-III) antibody and immunodeficiency conditions in homosexual men. Lancet ii: 711-715, 1984.

Goedert, J. J., Sarngadharan, M. G., Eyster, M. E., Weiss, S. H., Gallo, R. C. and Blattner, W. A.: Antibodies reactive with human T-cell leukemia viruses (HTLV-III) in the serum of hemophiliacs receiving Factor VIII concentrate. Blood 65: 492-495, 1985.

Greaves, M. F., Verbi, W. Tilley, R., Lister, T. A., Habeshaw, J., Guo, H. G., Trainor, D. C., Robert-Guroff, M., Blattner, W. A., Reitz, M. and Gallo, R. C.: Human T-cell leukaemia virus (HTLV) in the United Kingdom. Int. J. Cancer 33: 795-806, 1984.

Greaves, M. F., Verbi, W., Tilley, R., Lister, T.A., Robert-Guroff, M., Blattner, W. A., Reitz, M., and Gallo, R. C.: Human T-cell leukemia virus in immigrants to the United Kingdom. In Gallo, R. C., Essex, M. E. and Gross, L. (Eds.): Cancer Cells: Human T-Cell Leukemia/Lymphoma Viruses. New York, Cold Spring Harbor Laboratory, 1984, Chapter 3, pp. 297-306.

Hahn, B. H., Popovic, M., Kalyanaraman, V. S., Shaw, G. M., LoMonico, A., Weiss, S. H., Wong-Staal, F. and Gallo, R. C.: Detection and characterization of an HTLV-II provirus in a patient with AIDS. In Gottleib, M. and Groopman, J. (Eds.): Acquired Immune Deficiency Syndrome. New York, Alan R. Liss, 1984, pp. 73-81.

Jones, E. H., Biggar, R. J., Nkrumah, F. K. and Lawler, S. D.: Study of the HLA system in Burkitt's lymphoma. Human Immunol. III: 207-210, 1980.

Kestens, L., Biggar, R. J., Melbye, M., Sarin, P., deFeyter, M., Paluko, L. and Gigase, P. L.: Cellular immunity in healthy HTLV-III antibody positive subjects from Eastern Zaire. N. Engl. J. Med. (In Press).

Kestens, L., Melbye, M., Biggar, R. J., Stevens, W. J., Piot, P., Muynck, A. D., Taelman, H., deFeyter, M., Paluku, L. and Gigase, P. L.: Endemic African Kaposi's sarcoma is not associated with immunodeficiency. Int. J. Cancer (In Press).

Landesman, S. H., Ginzburg, H. M. and Weiss, S. H.: The AIDS epidemic. N. Engl. J. Med. 312: 521-525, 1985.

Madhok, R., Melbye, M., Lowe, G. D., Forbes, C. D., Froebel, K. S., Bodner, A. J. and Biggar, R. J.: Evidence for recent HTLV-III (AIDS-agent) infection in sequentially followed (1974-84) haemophiliacs. Lancet (In Press).

Mann, D. L., DeSantis, P., Newman, M., Gibbs, N., Popovic, M., Sarngadharan, M. G., Gallo, R., Clark, J. and Blattner, W.: Immunoglobulin "captured" from chronic lymphocytic leukemia cells has antibody activity to HTLV-I, -II, -III. Nature (In Press).

Mann, D. L., Popovic, M., Murray C., Neuland, C., Strong, D. M. and Blattner, W. A.: Cell surface antigen expression in cord blood lymphocytes infected with HTLV. J. Immunol. 131: 2021-2024, 1983.

Melbye, M., Froebel, K. S., Madhok, R., Biggar, R. J., Sarin, P., Stenbjerg, S., Lowe, G. D. O., Forbes, C. D., Goedert, J. J., Gallo, R. C. and Ebbesen, P.: HTLV-III seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the U.S.A. Lancet ii: 1444-1446, 1984.

Melbye, M., Ingerslev, J., Biggar, R. J., Alexander, S., Sarin, P., Goedert, J. J., Zachariae, E., Ebbesen, P. and Stenbjerg, S.: Anal intercourse as a possible factor in heterosexual transmission of HTLV-III to spouses of hemophiliacs. N. Engl. J. Med. 312: 857, 1985.

Melbye, M., Biggar, R. J., Chermann, J. C., Montagnier, L., Stengbjer, S., Ebbesen, P.: High prevalence of lymphadenopathy virus (LAV) in European haemophiliacs. (Letter to the Editor) Lancet ii: 40-41, 1984.

Melbye, M., Biggar, R. J. and Ebbesen, P.: Immunologic studies in healthy Danish homosexual men. Antibiot. Chemother. 32: 117-126, 1984.

Melbye, M., Biggar, R. J., Ebbesen, P., Sarngadharan, M. G., Weiss, S. H., Gallo, R. C. and Blattner, W. A.: Seroepidemiology of HTLV-III antibody in Danish homosexual men: Prevalence, transmission, and disease outcome. Br. Med. J. 289: 573-575, 1984.

Melbye, M., Froebel, K. S., Madhok, R., Biggar, R. J., Sarin, P., Stenbjerg, S., Lowe, G. D. O., Forbes, C. D., Goedert, J. J., Gallo, R. C. and Ebbesen,

P.: HTLV-III seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the U. S. A. Lancet ii: 1444-1446, 1984.

Melbye, M., Ingerslev, J., Biggar, R. J., Alexander, S., Sarin, P., Goedert, J. J., Zachariae, E., Ebbesen, P. and Stenbjerg, S.: Anal intercourse as a possible factor in heterosexual transmission of HTLV-III to spouses of hemophiliacs. N. Engl. J. Med. 312: 857, 1985.

Melbye, M., Skinhoj, P., Nielsen, N.H., Vestergaard, B. F., Ebbesen, P., Hansen, J. P. H. and Biggar, R. J.: Virally associated cancers in Greenland: Frequent hepatitis B virus infection but low primary hepatocellular carcinoma incidence. J. Natl. Cancer Inst. 73: 1267-1272, 1984.

Merino, F., Robert-Guroff, M., Clark, J., Biondo-Bracho, M., Blattner, W. A. and Gallo, R. C.: Natural antibodies to human T-cell leukemia/lymphoma virus in healthy Venezuelan populations. Int. J. Cancer 34: 501-506, 1984.

Nowell, P. C., Finan, J. B., Clark, J. W., Sarin P. and Gallo, R. C.: Karyotypic differenes between primary cultures and cell lines from HTLV-positive leukemia/lymphoma. JNCI 73: 849-852, 1984.

Pottern, L. M. and Blattner, W. A.: Etiology and epidemiology of multiple myeloma and related disorders. In Wiernik, P. H., Canellos, G. P. and Kyle, R. A. (Eds.): Neoplastic Diseases of the Blood and Blood-Forming Organs. New York, Churchill Livingstone, Chapter 7, 1985, pp. 413-429.

Rinaldo, C. R., Kingsley, L. A., Lyter, D. W., Rabin, B. S., DeBiasio, R. L., Atchison, R. W., Valdiserri, R. O., Zhao, J-Q, Lin, T., Bodner, A. J., Saxinger, W. C. and Weiss, S. H.: Association of human T cell lymphotropic retrovirus III with risk factors for AIDS in gay and bisexual men in low incidence area for AIDS. N. Engl. J. Med. (In Press).

Robert-Guroff, M., Schupbach, Blayney, D. W., Kalyanaraman, V. S., Merino, F., Lanier, A., Sarngadharan, M. G., Clark, J., Saxinger, C., Blattner, W. A. and Gallo, R. C.: Sero-epidemiologic studies on HTLV-I. In Gallo, R. C., Essex, M. E., Gross, L. (Eds.): Cold Spring Harbor Book on HTLV 3. New York, Cold Spring Harbor Laboratory, 1984, pp. 285-295.

Robert-Guroff, M., Weiss, S. H., Giron, J., Jennings, A. M., Ginzburg, H. M., Margolis, I., Blattner, W. A. and Gallo, R. C.: Associations to HTLV-I, -II, and -III with soft tissue infections in intravenous drug abusers from an AIDS endemic region. N. Engl. J. Med. (In Press).

Rowley, J. D., Haren, J. M., Wong-Staal, F., Franchini, G., Gallo, R. C. and Blattner, W. A.: Chromosome pattern in cells from patients positive for Human T-cell leukemia virus. In Gallo, R. C., Essex, M. E. and Gross, L. (Eds.): Cancer Cells: Human T-Cell Leukemia/Lymphoma Viruses. New York, Cold Spring Harbor Laboratory, 1984, Chapter 3, pp. 85-89.

Saxinger, W. C., Blattner, W. A., Guo, H. G., Hoh, M. W., Moghissi, J., Lapin, B. A., Yakovleva, L. A., Li, Y. W., Cheng, S. F., Lu, M. R., Kalyanaraman, V. S., Sarngadharan, M. G., Ito, Y. and Gallo, R. C.: Diversity of HTLV-related primate T-cell retroviruses: Species and host range. Int. J. Cancer (In Press).

Saxinger, W. C., Ito, Y., Li, Y. W., Cheng, S. F., Lu, M. Y., Blattner, W. A., L, Lapin, B. A., Yekeulenua, L. A., Sarngadharan, M. G., Kalyanaraman, V. S. and Gallo, R. C.: Distribution of antibodies to HTLV in a multiplicity of old world primates. Nature (In Press).

Saxinger, W. C., Lange-Wantzin, G., Thomsen, K., Lapin, B., Yakovleva, L., Li, Y-W, Guo, H-G, Robert-Guroff, M., Blattner, W. A., Ito, Y. and Gallo, R. C.: Human T-cell leukemia virus: a diverse family of related exogenous retrovirus of humans and old world primates. In Gallo, R. C., Essex, M. E. and Gross, L. (Eds.): Cancer Cells: Human T-Cell Leukemia/Lymphoma Viruses. New York, Cold Spring Harbor Laboratory, 1984, Chapter 3, pp. 323-330.

Saxinger, W. C., Blayney, D. W., Postal, M., Blattner, W. A., Moghissi, J. and Gallo, R. C.: Risk of infection of laboratory workers with the Human T-Cell Leukemia Virus (HTLV). Lancet ii: 274-275, 1983.

Saxinger, W., Blattner, W. A., Levine, P. H., Clark, J., Biggar, R., Hoh, M., Moghissi, J., Jacobs, P., Wilson, L., Jacobson, P., Crookes, R., Strong, M, Ansari, A.A., Dean, A.G., Nkrumah, F. K., Mourali, N. and Gallo, R. C.: Human T-cell leukemia virus (HTLV-I) antibodies in Africa. Science 225: 1473-1476, 1984.

Schonheyder, H., Melbye, M., Biggar, R. J., Ebbesen, P., Neuland, C. Y. and Stenderup, A.: Oral yeast flora and antibodies to Candida albicans in homosexual men. Mykosen. Berlin, Grosse Verlag, 1984, pp. 539-544.

Schupbach, J., Kalyanarman, V. S., Sarngadharan, M. G., Bunn, P. A., Blayney, D. W. and Gallo, R. C.: Demonstration of the viral antigen p24 in circulating immune complexes of two patients with human T-cell leukemia/lymphoma virus (HTLV) positive lymphoma. Lancet i: 302-305, 1984.

Weiss, S. H. and Goedert, J. J.: Screening assays for HTLV-III antibodies. American Medical Association. (In Press).

Weiss, S. H., Goedert, J. J., Sarngadharan, M. G., Bodner, A. J., Biggar, R. J., Clark, J. W., Giron, J. A., Dodd, R. Y., Melbye, M., Masur, H., Gelmann, E. P., Lane, H. C., Fauci, A. S., Hoofnagle, J. H., Simberkoff, M., Winn, D. M., Greene, M. H., Saxinger, C. W., Robert-Guroff, M., Gallo, R. C. and Blattner, W. A.: Screening test for HTLV-III (AIDS agent) antibody: Specificity, sensitivity and applications. JAMA 253: 221-225, 1985.

Whang-Peng, J., Bunn, P. A., Knutsen, T., Kao-Shan, C. S., Broder, S., Jaffe, E. S., Gelmann, E., Blattner, W. A., Lofters, W., Young, R. C. and Gallo, R. C.: Cytogenetic studies in human T-cell lymphoma virus (HTLV)-positive leukemia/lymphoma in the United States. JNCI 74: 357-369, 1984.

Williams, C. K., Saxinger, W. C., Alabi, G. O., Junaid, T. A., Blayney, D. W., Greaves, M. F., Gallo, R. C. and Blattner, W. A.: HTLV-associated lymphoproliferative disease: report of 2 cases in Nigeria. Br. Med. J. 288: 1495-1496, 1984.

ANNUAL REPORT OF

THE RADIATION EPIDEMIOLOGY BRANCH

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

This is the second 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. No personnel changes have occurred during this past year. However, the Branch continues to attract visiting scientists from a number of countries for relatively short periods of intense collaboration. This past year, visiting scientists have come from Japan, Sweden, Denmark, England, Canada, Israel, and the People's Republic of China.

RESEARCH PROGRAM:

Studies of populations exposed to ionizing radiation are being conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk and to provide insights into carcinogenic mechanisms. An immediate practical need is for risk estimates on which to base decisions about the use of nuclear and radiological technology in medicine and industry.

Medical Exposure Studies: Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. The only evidence that a cancer can be induced by ionizing radiation for relatively insensitive tissues comes from patient populations given high-dose, partial body, therapeutic irradiation. For other sites, the best evidence on low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures.

A case-control study was conducted in a population of over 32,000 twins born in Connecticut 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. A two-fold excess risk was associated with prenatal x-ray, suggesting that the

association is due to radiation rather than the indications for pelvimetry. A feasibility study to conduct a similar investigation of over 100,000 twins in Sweden was also successfully completed, and a case-control study was initiated which will include approximately 100 cases of childhood cancer.

An international study of cervical cancer patients, including over 200,000 women treated by radiation or surgery, is nearing completion. For the first time, radiation regimens used to treat cervical cancer patients were found to be associated with a small, but significant, increased risk of leukemia. This small risk for leukemia may have been associated with low doses of radiation absorbed by bone marrow outside the pelvis, since bone marrow in the pelvis was probably destroyed or rendered inactive by the very large therapeutic exposures. Large radiation doses did not dramatically alter the risk of developing other second cancers, and at most only about 5% of 3,300 second malignancies could be attributed to radiation. Second cancers found to be associated with radiation included the bladder, rectum, uterine corpus, ovary, small intestines, bone, connective tissue and multiple myeloma, but not stomach, colon, liver and gallbladder, melanoma or chronic lymphocytic leukemia, despite substantial exposures. Ovarian damage caused by radiation may have been responsible for a low breast cancer risk, which was evident even among post-menopausal women. After a minimum latent period of about 10 years, the expression period for radiation-induced solid tumors appeared to continue to the end of life. Radiation-induced cancers did not tend to occur earlier than other naturally occurring cancers. Women under 30 or over 50 years of age when irradiated were at greatest absolute risk for cancer induction. A small excess of thyroid cancer was possibly associated with relatively low-dose exposure, but second cancers of other sites that received relatively low doses of radiation were either not increased beyond expectation or were elevated due to exposures to other strong risk factors such as cigarettes or alcohol. Ongoing investigations include case-control studies with individual dosimetry determinations, and chromosome, hormone, and pathology investigations.

Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhance the chance of detecting increased risks due to therapy. The study of 3,000 children treated for lymphoid hyperplasia with radiation or surgery in Boston is nearing completion. Physical examinations had been performed on more than 1,000 patients to determine more accurately the risk of thyroid nodules, and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. Preliminary analyses indicate an excess of both thyroid cancer and nodules in the exposed population. A further follow-up of 10,000 children irradiated for ringworm of the scalp in Israel, and 15,000 matched comparison persons, revealed an excess of thyroid cancer and thyroid nodules following doses on the order of nine rads, as well as elevated risks of brain tumor and leukemia. A biochemical epidemiologic study has been developed to evaluate whether the risk of thyroid cancer associated with such a low dose might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia telangiectasia is a genetic disorder relatively common

among North Africans; North African immigrants were found to be at highest relative risk for radiogenic thyroid disease in this study.

Over 9,000 persons who survived at least two years after a diagnosis of childhood cancer in 13 hospitals in the U.S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and controls to quantify the risks associated with radiation or chemotherapy treatments. Detailed dosimetry has been performed to estimate radiation doses to individual organs or tissues. Among second malignancies, bone cancer was associated with high-dose radiation therapy as evidenced by a strong dose-response relationship. Patients treated for retinoblastoma, a heritable disease associated with a propensity for developing subsequent osteosarcomas, were not at unusually high relative risk for radiogenic bone cancer when compared to children treated for other malignancies. Among patients who developed leukemias subsequent to treatment for childhood cancer, the excess risk was due almost entirely to alkylating agents and no elevated risk was associated with radiotherapy.

A population-based case-control study of thyroid cancer in Connecticut was analyzed. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978 and 1980, and on 285 controls. A high risk of thyroid cancer was associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. Few persons born after 1945 reported prior radiotherapy, a finding consistent with the declining use of radiation to treat benign conditions in the 1950s. Consumption of vegetable goitrogens appeared to decrease risk. Among women who received radiotherapy, subsequent live births appeared to enhance risk. Approximately 9% of all thyroid cancers could be attributed to prior childhood head and neck irradiation. Other factors showing positive associations with thyroid cancer included late age at menarche, multiparity and miscarriage among women who developed thyroid cancer prior to age 35; and a previous history of thyroid nodules, goiter and benign breast disease.

A second mail questionnaire follow-up of women who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 was conducted and reaffirmed that repeated, relatively low radiation doses pose some future risk of breast cancer, that the risk may be cumulative, that adolescence is an especially sensitive age, and that older women may be at low risk of radiogenic breast cancer. The 40-year cumulative actuarial risk of developing breast cancer was estimated to be 9% among women exposed to greater than 100 rads as compared to 4% for women not subjected to repeated fluoroscopic chest examinations. A new cohort study of 4,000 female tuberculosis patients in Massachusetts found a modest elevation of breast cancer incidence associated with a mean breast dose of 66 rads. Additional studies are being completed in Massachusetts, Connecticut, and Denmark to clarify further the carcinogenic effect of multiple low-dose x-ray exposures in both men and women.

A significant risk of developing a second breast cancer was found among 27,000 breast cancer patients in Connecticut; case-control studies of long-term

survivors are being conducted in Connecticut and Denmark to learn whether the increased risk might be related to radiation therapy, especially among women treated after age 40. Adenocarcinoma of the uterus was linked to radiotherapy for the first time in a case-control study of cancer of the uterine corpus following treatments for breast cancer. Among 12,000 patients treated for uterine corpus cancer, a significant risk of subsequent leukemia was found among irradiated persons, but not for patients receiving surgery alone. Studies of multiple primary cancers in Connecticut suggested that rectal cancer was increased following radiation treatment of female genital cancers, and that second cancers of the bone and connective tissues were a consequence of high-dose radiotherapy for several sites.

A variety of analytic studies are underway. Using the resources of pre-paid health plans in California and Oregon, 2,000 cases of leukemia and lymphoma and 2,000 controls have been identified; and long-term histories of diagnostic x-ray exposures were obtained to evaluate the possible association with radiation dose to active bone marrow. A feasibility study of 1,600 patients treated for scoliosis in four Minnesota hospitals is being conducted to evaluate the possible risk of breast cancer associated with large numbers of spinal x-ray examinations performed during adolescence to monitor spinal curvature. A study of the carcinogenic effects of radiation therapy for gastric ulcer has been initiated. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and further studies have been initiated, including a second follow-up of 36,000 patients treated with radioactive iodine or surgery for thyrotoxicosis in the United States and collaborative studies of approximately 60,000 persons who received diagnostic or therapeutic doses of radioactive iodine in Sweden. A feasibility study to evaluate over 30,000 patients treated with diagnostic doses of radioactive iodine in Demark was completed. Women are being studied who received radiation therapy for benign gynecological disorders in Massachusetts, New York, Rhode Island, Connecticut, and Sweden. A two day workshop was conducted to discuss areas of collaboration and methods for combining collected data, including data from additional series in Scotland and England. 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 has been formed to work with the Branch on dosimetry problems. In addition, computer simulation codes, developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health (FDA), have been used effectively to estimate radiation doses.

Atomic Bomb Survivors Studies: The life-span study (LSS) sample of 82,000 A-bomb survivors plus 26,000 non-exposed residents is perhaps the single most valuable source of epidemiological information on radiation carcinogenesis in man. The Radiation Effects Research Foundation (RERF) has sole access to the LSS sample and has on file individual radiation dose estimates and current addresses for nearly all sample members. A virtually complete mortality follow-up is maintained at the death certificate level. A clinical subsample, which includes most of the heavily exposed survivors, has been offered biennial medical examinations since 1958; about 12,000 have participated on a

regular basis. An autopsy program, which has gradually shifted from an in-house activity to one depending mainly on support from major city hospitals, has resulted in the accumulation of an extensive collection of tissue specimens. RERF plays the major role in the tumor, tissue, and leukemia registries in the two cities which supply the bulk of the diagnostic information for incidence and case-control studies. The Branch seeks to foster a close, long-term, scientific relationship with the RERF through a program of collaborative studies supported by a multi-year research contract with the U.S. National Academy of Sciences, in effect since 1980.

A new incidence survey through 1980 identified 564 breast cancer cases. Breast cancer risk was strongly related to radiation dose for exposure at all ages prior to 40, but not at older ages. The existence of an excess risk following exposure in early childhood was not known previously. A case-control interview study of breast cancer to examine possible interactions or synergisms between radiation and other environmental or host factors in the causation of breast cancer is being analyzed. An interview case-control study of over 500 lung cancer cases found the joint effect of radiation and smoking to be additive, in contrast to the multiplicative effect seen for uranium miners.

The wave-like distribution of leukemia risk over time following exposure was found to be in marked contrast to that for cancers of the breast, lung, and digestive organs for which the distribution in time of radiation-induced cancers appeared similar to that for non-radiation-induced cancers. It seems that radiation exposure increases cancer risk, but that the additional cancers of these sites appear at ages when cancers normally occur and are distributed over time as one might expect on the basis of population rates.

Incidence and case-control studies of colon cancer and rectal cancer are being conducted. Preliminary analyses indicate a strong dose-response relationship for colon cancer, especially the sigmoid colon, but none for rectal cancer. A feasibility study of thyroid cancer was completed. Because the current status of radiation dose estimates for the atomic bomb survivors is in flux, there is consequent uncertainty about risk estimates. Enough is known, however, to calculate new dose estimates for persons exposed in the open or in simple shielding configurations, and a collaborative effort is underway to use this subset in making cancer risk estimates. Laboratory investigations are being performed on cultured fibroblasts derived from skin biopsies of high-dose and low-dose breast cancer cases and controls. This investigation is intended to examine the possibility that dose-response relationships reflect not only the kinetics of radiation damage to the DNA of individual cells, but also individual differences in sensitivity to radiation damage. Planning has also been completed for hormonal and micronutrient assays of stored serum samples for cancer cases and controls. Chromosomal materials have been exchanged with U.S. investigators to evaluate comparability of chromosomal aberration assays used for medically irradiated populations under study by the Branch.

Occupational and Environmental Exposure Studies: Although the possibility of increased cancer risk associated with chronic occupational exposure to low-LET

radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk. Although other Governmental agencies sponsor large-scale investigations of occupationally exposed workers, efforts in this area have recently increased within our program with the addition last year of two new staff members with experience in occupational studies.

The existence since 1926 of a professional registry of over 170,000 medical x-ray technologists offered a unique opportunity to study a large and well-defined population occupationally exposed to highly fractionated low-dose radiation. The two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, are being evaluated. In addition, a feasibility study of nuclear power workers is being developed; studies of persons occupationally exposed to uranium are being completed; and tracing support for a study of radium dial painters employed prior to World War I is being considered. A study of thyroid nodules associated with high natural background areas in China is being developed. Radon exposure in the home has been suggested as an important risk factor for lung cancer, dosimetry studies have been initiated, and a collaborative case-control study is ongoing in Sweden.

An analysis of county-specific mortality data for the state of Utah, 1950-1980, provided no support for published claims of extremely high cancer risk among long-term residents of the three southwestern counties closest to the Nevada Test Site, and exposed to radioactive fallout from atomic bomb tests in 1953, 1955, and 1957. Results were, in fact, grossly discordant with the purported excess risks, and only for leukemia was there a suggestion of a risk greater than that for the remainder of the state.

Drug Studies: This project focuses on the long-term health effects of drugs, especially therapeutic agents, as they may apply to carcinogenicity. Patients treated in randomized clinical trials have been studied, resources of the Surveillance, Epidemiology, and End Results (SEER) Program have been employed, and collaborative studies have been initiated with several institutions. In collaboration with the Environmental Epidemiology Branch and the Division of Cancer Treatment, a systematic study of therapeutic drugs continues. Occasionally it is possible to evaluate other drug exposures in populations that have been studied primarily for other reasons.

The risk of acute non-lymphocytic leukemia and preleukemia was previously evaluated in 3,600 patients with gastrointestinal cancer treated in nine randomized clinical trials. Patients given methyl-CCNU, a nitrosourea, as adjuvant therapy, were found to be at high risk of developing leukemia. This study provided the first quantitative evidence that nitrosoureas are leukemogenic in man and confirms previous observations that adjuvant chemotherapy with alkylating agents increases the risk of leukemia. Subsequent analyses indicate that the risk of developing a leukemic disorder was directly related to the total dose per surface area administered. A study of women treated

with melphalan or chlorambucil for ovarian cancer in five randomized clinical trials also found a very high risk of leukemia. This study was expanded to include patients treated at the Mayo Clinic and the M. D. Anderson Hospital, and dose-response analyses are underway. Comparative analyses indicate that the leukemic potential of cyclophosphamide is significantly lower than that of melphalan. Studies of low-dose adjuvant chemotherapy did not find an increase of leukemia following exposure to antimetabolites such as 5-FU. Ongoing studies include the evaluation of patients with colorectal cancer and lung cancer who have received nitrogen mustard, cytoxan, methotrexate, and CCNU in the Veterans Administration clinical trials system; and an evaluation of patients treated with thioTEPA and 5-FU in early clinical trials of breast cancers.

A case-control study of 220 children with second malignant neoplasms and 400 controls is currently under analysis to evaluate the relationship between therapy received for the first malignant neoplasm and the development of the second cancer. These children were treated with a wide range of chemotherapy agents. The risk of secondary leukemia was found to be due almost entirely to alkylating agent therapy for the initial primary cancer, and no increased risk was found for radiation therapy. Alkylating agents were also found to be associated with a four-fold risk of subsequent bone cancer, suggesting for the first time that chemotherapy may increase the risk of solid tumor development among long-term survivors.

Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a nine-fold increased risk of acute non-lymphocytic leukemia was found. The increased risk of leukemia first appeared 2 years after the breast cancer diagnosis, was highest in 5-year survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1). Detailed case-control studies are being conducted in Connecticut to clarify the possible association of leukemia risk among breast cancer patients.

Analysis of data from the Breast Cancer Detection Demonstration Project showed that women who used thyroid hormones for treatment of thyroid disease and those who used them for other reasons (primarily weight loss or fertility problems) were not at significant risk of breast cancer. Women with untreated hyperthyroidism or goiter, however, appeared to be at a significantly reduced risk. Data from a case-control study of breast cancer patients who developed endometrial cancer indicated a significant risk associated with estrogen therapy as well as post-menopausal estrogens. Commonly used drugs, e.g., oral contraceptives, menopausal estrogens, antihistamines, sleeping pills, antibiotics, and medicine for severe diarrhea, were not found to be related to thyroid cancer in a population-based case-control interview study. Use of diuretics, however, appeared associated with a 1.7-fold risk. A feasibility study has been initiated of epileptic patients and their offspring to evaluate the possible transplacental carcinogenicity of anti-convulsive drugs. The possible late effects following isoniazid therapy for pulmonary tuberculosis will be evaluated further in large-scale mortality studies in Connecticut and Massachusetts.

Multiple Primary Cancer Studies: The Branch conducts a variety of studies to evaluate the risk of developing a second malignant neoplasm following treatment for an initial primary cancer. Such studies are conducted to evaluate treatment effects, generate hypotheses about common etiologies and provide insights into mechanisms of carcinogenesis. The SEER program and other cancer registries have been used to identify second primary cancers in persons with initial cancers of the breast, testis, endometrium, and cervix. Among 1,330 men with testis cancer, a two-fold risk of developing a second primary was observed. Radiotherapy and other treatments were associated with only a small proportion of the excess second cancers, suggesting that most of the risk is due to factors other than therapy.

A joint monograph on multiple primary cancers, focusing on long-term survivors, is being prepared in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. Cancer patients in Connecticut were found to have a 31% increased risk of developing a second primary cancer, which rose to 49% among those surviving for more than 30 years. Over one million person-years of observation were recorded, and the excess risk of developing a new cancer was 3.5 per 1000 persons per year. Tissue susceptibility and common carcinogenic exposures were likely explanations for the frequent occurrence of many second cancers, particularly those known to be related to cigarette smoking, alcohol consumption, or both. Persons with epithelial cancers of the lung, larynx, esophagus, buccal cavity and pharynx, for example, were particularly prone to developing new epithelial cancers in the same or contiguous tissue. A notable finding was the very high risk of cancers of the lung, larynx, buccal cavity and pharynx observed among cervical cancer patients, suggesting the possiblity of a common etiology with cigarette smoking. The intriguing association between cancers of the colon, uterine corpus, breast and ovary was confirmed in the Connecticut data, indicating the possible influence of hormonal or dietary factors. Patients with prostate cancer had a significantly low risk for second cancer development, which may reflect an underascertainment of second primaries in patients of advanced age. Radiotherapy may have caused second cancers of the rectum and other sites among patients with female genital tract cancers, and leukemia was seen in excess after radiotherapy for uterine corpus cancer. In addition, chemotherapy was associated with an increased risk of acute non-lymphocytic leukemia among patients with multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary. Large numbers of patients with cancers of the rarer sites, i.e., of the eye, were available for study; and for most of these sites, a high risk of second tumors was found which persisted over time. Numerous new associations were identified for future study.

Biochemical Studies: A number of biochemical studies have been added to epidemiologic investigations to determine the usefulness of somatic aberrations in circulating lymphocytes as biological dosimeters. Cytogenetic aberration data in persons with partial-body irradiation are being evaluated in four medically-irradiated populations in collaboration with the Oak Ridge Associated Universities. The objectives are to determine the type and frequency of chromosome aberrations and to compare dose-response relationships with those seen in A-bomb survivors who experienced total body exposures; and

to determine the persistence of effects in relation to sex, age at exposure, dose, dose fractionation, and radiation quality. Populations being evaluated include persons irradiated for enlarged tonsils or thymic glands as children, cervical cancer patients treated with radiation, and tuberculosis patients who received multiple chest fluoroscopies. A small, but statistically significant, increase in translocations and inversions was found in tonsil patients treated by radiotherapy when compared with those treated by surgery. Large differences in the frequency of similar aberrations were found between exposed and nonexposed cervical cancer patients. Among persons irradiated for enlarged tonsils, serum tests and measurements of thyroglobulin concentrations have been made, including T3, T4, TBGI, calcium, TSH, and AMA. To evaluate an unusual lowering of breast cancer risk among post-menopausal women following ovarian irradiation for cervical cancer, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Cultured skin fibroblasts from several irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancers. Populations studied include the atomic bomb survivors and the Israeli patients irradiated for ringworm of the scalp. A study is planned among atomic bomb survivors of the relationship between cancer induction and levels of hormones and micronutrients in sera obtained prior to cancer diagnosis.

Methodologic Studies: This project area focuses on methods for increasing the information from existing bodies of data and for treating analytic problems that arise during the course of other studies. For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an approach was applied to breast cancer incidence data and is to be applied with respect to thyroid cancer incidence data from several exposed populations.

Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. Random error in individual dose estimates was found to bias dose-response analyses based on grouped data. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of base-line and excess risk are compared as well as integrated risk over the entire period of observation. Approximate 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. Our text of statistical methods useful in epidemiologic studies has proven so popular that a third edition was recently published.

Reviews: A major role of the Branch is to continue to provide comprehensive and critical reviews of the health effects of ionizing radiation. Such reviews include a general overview, a review of cancers following medical irradiation for benign gynecologic disease, an evaluation of the statistical and epidemiologic issues concerning estimation of cancer risk from low doses of ionizing radiation, and overviews on the importance of latent period, risk projection and time-response models in estimating cancer risks. Following congressional directive, the Branch participated in the development of radio-epidemiologic tables to provide probabilities that a given dose of radiation has caused a specific cancer in an individual. These critical reviews help the Branch stay current in the area of radiation carcinogenesis and suggest new directions for the research programs.

OTHER ACTIVITIES:

The Branch continues to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities. Branch members have served as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Department of Defense, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the Three Mile Island Public Health Advisory Group, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the World Health Organization, and two NIH committees chartered for the purpose of preparing radioepidemiologic tables for the computation of cancer risk following radiation exposure. At times staff members have become heavily involved in controversial public policy issues and debates, most recently with the issue of compensation of veterans and other persons exposed to purported low levels of radiation fallout from nuclear weapons tests in the western United States.

In collaboration with the Clinical and Environmental Epidemiology Branches, the Radiation Epidemiology Branch continues to identify and utilize epidemiologic resources best available at the national or international level. Cost-efficient methods for tracing persons exposed to carcinogens in the past have been evaluated, and various state and national record systems have been used for epidemiologic purposes (e.g., Social Security Administration, Internal Revenue Service, National Center for Health Statistics, Health Care Finance Administration, U.S. Post Office, Veterans Administration, and various state departments of vital statistics). To extend state mortality coverage prior to 1979 when the National Death Index began, meetings and negotiations have been held with several state and national committees, and a feasibility study has been initiated. To utilize more fully resources that are available in cancer registries in the United States and other countries, new initiatives have been made for collaborative record linkage studies. The Branch also provides on-the-job training of staff at the post-doctoral level, supervises graduate students during NIH summer training programs, provides field research opportunities for doctoral candidates at schools of public health, and collaborates with visiting scientists from a number of countries, including Denmark, Sweden, Israel, and Japan.

New directions and ongoing research projects of the Radiation Epidemiology Branch undergo critical review. Oversight and evaluation is provided through weekly Branch meetings; monthly meetings with support services groups; frequent contact with other support services and collaborating groups; several working groups (e.g., drug studies); interagency committees; formal review mechanisms for the careful scrutiny of questionnaires and protocols by internal and external review committees; ad hoc external review groups for major studies (e.g., the International Radiation Study of Cervical Cancer Patients); and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors of the Division of Cancer Etiology.

SUMMARY REPORT

RADIATION EPIDEMIOLOGY BRANCH

PROGRESS ON RESEARCH CONTRACTS

The studies of radiation-induced cancers supported by the research contract mechanism (15 contracts, $1,548,212) are to strengthen the quantitative basis for risk estimation, especially at low doses, to improve the understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. Specific studies are discussed below.

Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis. The objectives of this study are to determine the incidence of cancer in 10,000 Israeli children irradiated for ringworm of the scalp, 10,000 nonexposed persons selected from the general population, and 5,000 nonexposed siblings. The methods employed are as follows: The study cohorts were previously identified from immigration records (1949-60) and the risk of thyroid cancer evaluated. Medical records in all 22 Israeli hospitals and records available in the Central Tumor Registry have been searched to determine malignant and benign tumors that developed in the exposed and comparison cohorts. Detailed dosimetry data have been obtained. Death certificates have been evaluated for those who have died, and the vital status as of 1981 has been determined for all enrolled persons. Malignancies of particular interest include thyroid, brain, parotid gland, breast, bone, lung, esophagus, larynx, skin, leukemia, and lymphoma. A preliminary report has indicated that increased rates of malignant (35 vs. 8.7 expected) and benign tumors of the thyroid, cancer of the brain (34 vs. 6.7), and leukemia (13 vs. 4.7) are associated with scalp irradiation during childhood. A draft paper on the mortality experience of these children was prepared. 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 two-year biochemical epidemiology extension was initiated in collaboration with the Clinical Epidemiology Branch. Cultured skin fibroblasts will be 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.

Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer. The objectives of this study are to determine whether radiotherapy for breast cancer increases the risk of a second primary breast cancer in the contralateral breast, and, if such a risk exists, to evaluate the dependence of risk on dose and age at exposure. Study subjects will be drawn from approximately 50,000 women with breast cancer reported to the population-based tumor registry in Denmark between 1943-1975. Cases will be all women with breast cancer who developed a second primary breast cancer ten or more years after treatment for the first malignancy. Controls will be women with a primary breast cancer who did not develop another breast cancer. One control will be matched to each case on age at initial breast cancer diagnosis,

calendar year of diagnosis, and survival time. Approximately 1,000 cases and 1,000 controls are available for study.

Cancer Risk in Patients Irradiated for Peptic Ulcer. The objectives of this study are to determine the risk of cancer in 2,054 patients treated by x-rays for peptic ulcer at the University of Chicago between 1937-1965, compared with 2,500 patients treated by surgery or other means during the same time period. Hospital and radiation therapy records are being used to identify the study cohorts. For those patients treated by x-rays, estimates of radiation doses to specific organs will be determined. Death certificates will be obtained for those who have died and the vital status, as of 1984, will be ascertained. Malignancies of particular interest include the stomach, pancreas, colon and lung.

Risk of Cancer Following Multiple Chest Fluoroscopies for Tuberculosis in Connecticut. The objectives of this program of study, which includes hospitals in Massachusetts, are to determine the long-term health effects of multiple low-dose radiation exposures in men and women and to estimate the risk of radiation-induced leukemia, lung cancer, and breast cancer. All eligible patients discharged alive from major Massachusetts and Connecticut State tuberculosis hospitals between 1930 and 1952 are being studied. Hospital records were abstracted to determine the extent of the tuberculosis and the number of fluoroscopic examinations performed on each patient. Death certificates have been obtained for most patients who have died. The Connecticut Tumor Registry has also been used to ascertain the incidence of cancer. Mail questionnaires were sent to living persons. Preliminary results from Connecticut are as follows: Abstract forms have been completed on the total population of 7,769 eligible patients; 4,139 (or 51%) are known to have died; 1,995 (or 26%) have been found alive and sent a mail questionnaire, of whom 964 (or 48%) have responded to date; 1,635 (or 21%) patients are not yet located; 686 cancers have been identified among 622 individuals, or 8% of the total population; and 2,915 (or 38%) patients received pneumotherapy with the associated multiple chest fluoroscopies, the average number of refills being about 30 per individual. From information obtained from the medical records, death certificates, and linkage with the Connecticut Tumor Registry files, 686 cancers were identified. This number does not include cancers that have been identified from the mail questionnaire, but does include 117 lung cancers, 48 breast cancers, 13 leukemias, 4 multiple myelomas, 31 esophageal cancers, and 3 thyroid cancers.

A Follow-up Study of Patients Treated for Hyperthyroidism. The objective of this study is to determine cancer and other causes of mortality in a cohort of 21,000 patients treated by ^{131}I for hyperthyroidism between 1946-1964. Mortality rates in the exposed cohort will be compared with those among 10,500 patients treated by thyroid surgery. This is the second follow-up study of a population identified in 18 hospitals in the U.S. and followed from 1961-1968. Radiation dosimetry estimates will be derived from the ^{131}I treatment records. This study is being conducted in four geographical areas of the U.S. (California, New York, Boston, and other U.S.). Malignancies of particular interest include thyroid, breast, salivary, leukemia, kidney and bladder. The risk of thyroid cancer associated with thyroid nodules will also be evaluated.

International Radiation Study to Evaluate the Risk of Radiation Exposure in Cervical Cancer--European Segment. The objectives of this study are to: (1) quantify the risk of radiogenic cancer in cervical cancer patients for sites that are not well studied, such as the stomach and pancreas; (2) evaluate the risk of low-level exposures to the breast and thyroid; and (3) evaluate the influence of host factors (such as age) on subsequent radiogenic risk. Over 200,000 women with cervical neoplasia who have been reported to one of 15 cancer registries are being evaluated for the risk of second malignancies. Case-control studies for specific cancer sites are being conducted to provide detailed information on radiation dose for risk assessment. More than 40,000 patients treated for cervical cancer in 14 European clinics are being evaluated for the occurrence of second cancers subsequent to radiotherapy. Radiation doses to body organs outside the pelvis are relatively low, under 100 rads, and can be accurately characterized. Detailed dosimetry information has been abstracted from hospital records. Morbidity and mortality are being determined through active follow-up. The cancer registry cohort analyses have been completed and published in the May 1985 issue of the Journal of the National Cancer Institute. Findings indicate excess risks, related to radiation, for cancers of the rectum, kidney, ovary, and corpus uteri, as well as acute nonlymphocytic leukemia and multiple myeloma. A deficit of breast cancer, possibly related to ovarian ablation, was also observed. Ongoing case-control studies will determine the extent to which cancer risk is related to radiation dose.

Thyroid Cancer Risk Following Diagnostic and Therapeutic ^{131}I Exposure. The objectives of this study are to determine the risk of thyroid cancer and other cancers following diagnostic and therapeutic ^{131}I exposure. This study is an extension and expansion of a previous study in Sweden. The new investigation (1) includes additional Swedish hospitals where ^{131}I was administered; and (2) extends patient follow-up. An estimated 45,000 patients exposed to diagnostic ^{131}I between 1950-1970 will be identified in seven hospital centers in Sweden. An estimated 20,000 patients treated by ^{131}I for hyperthyroidism and 6,000 patients treated by ^{131}I for thyroid cancer between 1951-1975 should also be identified at these same seven centers. Medical and therapy information will be abstracted from the patient hospital record. Follow-up will be conducted by record linkage with the Swedish Cause of Death Register (1951-1985) and the Swedish Cancer Registry (1958-1985). Malignancies developing in the first seven years of study (1951-1957) will be identified through death certificates. Expected numbers of malignancies will be calculated using age-, sex-, site-specific-, and calendar-time-specific-incidence data from the Cancer Registry or on the basis of mortality rates from the National Office of Vital Statistics.

Risk of Cancer in X-Ray Technologists. The objective of this study is to evaluate the long-term effects of chronic low-dose occupational exposures to radiation due to occupation among 170,000 radiologic technologists registered with the American Registry of Radiologic Technologists, in effect since 1926. Optical scan questionnaires were sent to the 140,000 active members to determine cancer incidence, and to obtain information on the use of dosimeters and on cancer risk factors, such as cigarette smoking. Over 50,000 questionnaires have been returned to date. Follow-up letter and/or telephone contact is encouraging even greater response. Additionally, almost 20,000 of

the 30,000 inactive members have been located. The remaining 10,000 continue to be traced using various methods and resources. Of those found, the living members are being sent questionnaires, while death certificates are being procured for the deceased. Preliminary findings suggest higher than expected incidences of thyroid cancers among this occupational group. Radiation exposures will be quantified, based on length of employment, film badge readings, and questionnaire responses. Excess cancer incidence and mortality will be evaluated in relation to radiation exposure.

Epidemiologic Studies of Cancer among A-bomb Survivors. The objectives of this collaborative study are to identify and quantify the possible interaction 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 82,000 A-bomb survivors and 26,000 non-exposed 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 studies in which epidemiologic factors other than radiation, as determined from existing records or by interview, are investigated. Reviews of diagnostic material by panels of pathologists are often employed in connection with the studies. Stored blood sera obtained prior to cancer diagnosis may be analyzed to investigate possible influences of hormonal, nutritional, and other factors. A major long-term goal of the project is to investigate ways of improving the completeness and diagnostic accuracy of cancer case ascertainment materials through the linkages with tumor and tissue registries, insurance records, contacts with hospitals and physicians, and other means.

A study of female breast cancer incidence has been completed and accepted for publication as an RERF technical report; other publications have appeared or are in preparation. Colorectal cancer incidence is currently being investigated by similar means. Case-control interview studies of breast, lung, colorectal, and thyroid cancers are in various stages of completion. Planning has been completed for hormonal and micronutrient assays of stored serum samples for cancer cases and controls, and research protocols have been submitted to the RERF protocol committee. A pilot study using cancer cases identified recently from death certificates has confirmed that, for cases in the Osaka region, there is a high probability of inclusion in the Osaka tumor registry. Pilot studies are planned for linkage with other tumor registries. Chromosomal materials are being exchanged between RERF and a contractor at Oak Ridge Associated Universities to investigate comparability of chromosomal aberration assays of medically irradiated populations under investigation by the Branch with those of A-bomb survivors studied at RERF. Skin fibroblasts are being obtained from recent breast cancer cases and controls, with high and low radiation doses. These fibroblasts are cultured at Brookhaven National Laboratory and assayed for sensitivity to cell-killing by gamma radiation.

The following findings have been obtained: breast cancer risk is strongly related to radiation dose for exposures at all ages prior to 40, but not at older ages; the existence of an excess risk following exposure in early childhood was not known previously. Proposed changes in the dosimetry used for the A-bomb survivor population seem unlikely to affect risk estimates or other inferences concerning radiation-induced breast cancer. Radiation and smoking appear additive in effect for the causation of lung cancer in A-bomb survivors. Colon cancer risk is strongly related to radiation dose; the relationship seems particularly strong for cancers of the sigmoid colon.

Prenatal X-ray Exposure and Childhood Cancer in Twins. The objective of this study, to be carried out collaboratively with the National Institute of Environmental Medicine in Stockholm, is to evaluate the relationship of prenatal x-ray exposure to subsequent incidence and mortality from cancer before the age of 16 years. Twins are especially suitable subjects for this study because, until recent times, women thought to be pregnant with twins were often x-rayed regardless of other medical indications for this procedure. Comparisons of prenatally x-rayed single-born subjects are thought to be confounded with the medical complications of pregnancy for which the radiologic investigation has been made. Twins are also suitable subjects because the high frequency of prenatal x-ray exposure leads to better statistical power of the comparison of exposed and non-exposed subjects for subsequent medical events in samples of limited size.

The study objectives can be carried out efficiently in Sweden because of the unique records resources there. A registry of twin births from 1886 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.

Pilot evaluations indicate that over 100 cases of childhood cancer will be available for study, and that with 200 comparison subjects, this sample size will be sufficient to detect a doubling of risk with a high probability. Information obtained and considered in the analysis will be the number and kind of x-ray exposures, stage of pregnancy at exposure, birthweight, duration of gestation, medical complications of pregnancy, and other variables that might confound the comparison. The material will also provide a means of comparing overall childhood cancer incidence among twins with that of single-born subjects, which is also relevant to the main objectives of this investigation.

Irradiation for Benign Menstrual Disease. The objectives of this study are to determine cancer incidence and mortality and estimate the risks of radiation-induced cancer in women treated for benign gynecological disorders (BGD). A study size of at least 9,000 exposed women should be sufficient to provide adequate statistical power to detect and evaluate dose-response relationships for radiogenic leukemia and solid tumors. Medical, therapeutic, and follow-up information is being abstracted from medical records in New York, Massachusetts, Connecticut, Rhode Island, and Sweden. Death certificates are

being obtained for those who died, and questionnaires will be sent to those who are alive. Collaborative mortality analyses will be made using data from two other British series of patients, and comparisons will be made with Connecticut population rates for cancer incidence and with women treated without radiation for BGD if a large enough cohort of unexposed women can be assembled. Organ-specific radiation doses will be determined for individual BGD patients.

Leukemia and Lymphoma Associated with Diagnostic X-Ray. The objective of this study is to quantify the risks of leukemia and lymphoma associated with radiation exposure from diagnostic x-rays. Using the resources of the Kaiser prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, approximately 2,000 leukemia and lymphoma cases were found diagnosed since the inception of these plans in the early 1940s. At least one matched control has been identified for each case. Complete medical record information on diagnostic x-ray exposures and other cancer risk factors has been abstracted for all subjects from Oakland and Portland (1,261 cases and 1,578 controls). Diagnostic x-ray exposures were converted to total radiation doses received by the active bone marrow, using estimates of exposure for x-ray procedures provided by an expert medical physicist from M. D. Anderson Hospital. Data from Portland and Oakland have been consolidated, and preliminary analyses performed. The Los Angeles data are expected shortly. (The contracts with the Kaiser Foundation Research Institute in Los Angeles [NO1-CP-11038], Oakland [NO1-CP-11037], and Portland [NO1-CP-11009], are listed under the Environmental Studies Section, Environmental Epidemiology Branch, DCE, EBP.)

RADIATION EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 85

RADIATION STUDIES

Institution/Principal Investigator/ Contract Number	Title
Chaim-Sheba Medical Center Elaine Ron, Baruch Modan NO1 CP 01042	Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis
Chicago, University of Melvin L. Griem NO1 CP 41011	Cancer Risk in Patients Irradiated for Peptic Ulcer
Danish Cancer Registry Ole M. Jensen NO1 CP 51037	Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer
Energy, Department of Brookhaven National Laboratory A. Bertrand Brill YO1 CP 40503	Thyroid Disease Following 131-I Therapy for Hyperthyroidism
Harvard University Richard R. Monson NO1 CP 31049	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders
Harvard University Richard R. Monson NO1 CP 41060	A Follow-up Study of Patients Treated for Hyperthyroidism
Health Research, Inc. Diane Cookfair NO1 CP 31048	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders
International Agency for Research on Cancer Rudolfo Saracci NO1 CP 11017	International Radiation Study to Evaluate the Risk of Radiation Exposure in Cervical Cancer--European Segment
Karolinska Institute Lars-Erik Holm NO1 CP 51034	Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure

Memorial Hospital for Cancer and Allied Diseases David Schottenfeld NO1 CP 41061	A Follow-up Study of Patients Treated for Hyperthyroidism
Minnesota, University of Jack S. Mandel NO1 CP 21015	Risk of Cancer in X-Ray Technologists
National Academy of Sciences Seymour Jablon NO1 CP 01012	Epidemiologic Studies of Cancer Among A-bomb Survivors
National Institute of Environmental Medicine Anders Ahlbom NO1 CP 51033	Prenatal X-ray Exposure and Childhood Cancer in Twins
Southern California, University of Susan Preston-Martin NO1 CP 41062	A Follow-up Study of Patients Treated for Hyperthyroidism
Yale University W. Douglas Thompson NO1 CP 01029	Risk of Cancer Following Multiple Chest Fluoroscopies for Tuberculosis

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04481-09 REB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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
	G. W. Beebe	Health Statistician	CEB	NCI
	D. A. Hoffman	Epidemiologist	REB	NCI
	Z. Hrubec	Expert Statistician	REB	NCI
	R. A. Kleinerman	Epidemiologist	REB	NCI
	E. B. Harvey	Staff Fellow	REB	NCI

COOPERATING UNITS *(if any)*
Radiation Effects Research Foundation, Japan (R. K. Boutwell, H. Kato); Department of Energy (R. Goldsmith); Danish Cancer Registry (O. Jensen); Chaim Sheba Medical Center, Israel (B. Modan, E. Ron)

LAB/BRANCH
Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
11.0	8.0	3.0

CHECK APPROPRIATE BOX(ES)

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

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

This project (1) examines cancer incidence and mortality among populations exposed to ionizing radiation, especially at low dose levels; (2) characterizes the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; and (3) examines, tests, and formulates models of radiation carcinogenesis to help define basic mechanisms. Groups studied include the Japanese A-bomb survivors, and several large populations with documented therapeutic (e.g., cervical cancer patients), diagnostic (e.g., tuberculosis patients), and occupational (e.g., x-ray technologists) exposures to ionizing radiation. Program members serve on committees advising the government as well as international agencies.

Results of studies suggest that (1) susceptibility to radiogenic breast cancer declines with increasing age at exposure, and children exposed under age 10 are at high risk; (2) repeated exposure to relatively low radiation doses pose some future risk of breast cancer; (3) the risk of radiogenic cancer may remain throughout life; (4) prenatal x-ray in twins increases the risk of childhood cancer; (5) children irradiated for benign conditions of the head and neck are at high risk of developing thyroid and brain neoplasia; (6) 9% of all thyroid cancers may be attributed to prior childhood head and neck irradiation; (7) radiotherapy for childhood cancer was associated with increased risks of subsequent bone cancer but not leukemia; (8) high-dose radiation to the pelvis induces fewer leukemias than other types of exposures; (9) ovarian damage caused by radiation may lower breast cancer risk, even among postmenopausal women; (10) chromosome aberrations following partial-body irradiation persist in circulating lymphocytes for over 30 years; (11) radiogenic colon cancer occurs in atomic bomb survivors but not in cervical cancer patients treated with radiation.

PROJECT DESCRIPTION

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

John D. Boice, Jr.	Chief	REB	NCI
Charles E. Land	Health Statistician	REB	NCI
Gilbert W. Beebe	Health Statistician	CEB	NCI
Daniel A. Hoffman	Epidemiologist	REB	NCI
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Elizabeth B. Harvey	Staff Fellow	REB	NCI
Stella G. Machado	Expert Statistician	REB	NCI
Zdenek Hrubec	Expert Statistician	REB	NCI
Jerome Wilson	Staff Fellow	REB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Nancy L. Eby	Epidemiologist (P-Authority)	REB	NCI
Katherine W. Chen	Computer Programmer	REB	NCI
Michele M. Morin	Epidemiologist	REB	NCI
Robert Goldsmith	Guest Researcher	REB	NCI
William J. Blot	Chief	BB	NCI
Linda M. Pottern	Epidemiologist	BB	NCI
Mark H. Greene	Deputy Chief	EEB	NCI
Margaret A. Tucker	Clinical Investigator	EEB	NCI
Joan V. Liebermann	Medical Staff Fellow	REB	NCI
John J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI

Objectives:

(1) To plan and conduct independent and cooperative epidemiologic research to identify and quantify the risk of cancer in populations exposed to ionizing radiation (e.g., x-rays) and non-ionizing radiation (e.g., ultraviolet light). Populations with documented therapeutic, diagnostic, occupational, environmental or military exposures are studied; (2) to characterize the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; (3) to conduct population studies to examine possible analogs of radiation carcinogenesis in man, such as the induction of cytogenetic abnormalities in circulating lymphocytes, and to integrate laboratory markers of radiation exposure and tissue response into epidemiologic studies designed to clarify the patterns of cancer risk and the mechanisms of action; (4) to develop statistical and epidemiologic methodologies to facilitate epidemiologic research, and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations; and (5) to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities.

Methods Employed:

Studies of exposed populations are conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms.

The relationship between cancer risk and radiation is an especially promising area for epidemiologic research, because quantitative descriptions of exposure are usually straightforward. As Doll has put it, "studies of the quantitative relationships between dose and effect, of the conditions which modify the effect of a specific exposure and of the time relations between duration of exposure, intensity of exposure, length of induction period and the rate of progress of the clinical disease will enable the epidemiologist to take part in formulating and testing hypotheses about the mechanisms by which cancer is produced" (Acta Un. Int. Cancr. 20: 747, 1964). The program of radiation studies is summarized in four project areas: Medical Exposures, Atomic Bomb Survivors, Occupational and Environmental Exposures, and Methodologic Studies.

A. Medical Exposures. Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. Radiation studies may be a particularly useful approach to understand the mechanism by which cancer is produced since quantitative descriptions of exposure are usually straightforward, an advantage not available for most other carcinogens. For specific, relatively insensitive tissues, the only evidence that a cancer can be induced by ionizing radiation comes from patient populations given high-dose, partial-body, therapeutic irradiation. For other sites, the best evidence on low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures. The radiation studies program tries to assure that maximum benefit is derived from existing epidemiologic resources, and attempts to initiate studies of populations not previously evaluated, but which offer unusual potential for new information. Eighteen medically irradiated populations are currently under study: women irradiated for cervical cancer, benign gynecologic disorders, breast cancer and endometrial cancer; children irradiated for lymphoid hyperplasia, retinoblastoma and other cancers, or tinea capitis; men irradiated for testis cancer or peptic ulcer; patients who received diagnostic radiographic procedures for tuberculosis or scoliosis; twins who received prenatal x-ray; leukemia and lymphoma patients who received prior diagnostic x-ray examinations; thyrotoxicosis and other patients treated with radioactive iodine; and patients given diagnostic doses of radioactive iodine.

Populations receiving therapeutic irradiation are described below.

1. The International Radiation Study of Cervical Cancer is a program of studies designed to provide new insights into radiation carcinogenesis and to increase the precision of current risk estimates. These investigations include cohort studies in cancer registries and individual clinics, case-control studies, dosimetry studies, chromosome studies, hormone studies, and pathology evaluations. The program evolved from a WHO-sponsored investigation of 30,000 women treated for cancer of the cervix uteri in nine different countries and clinically evaluated from 1960-1970. The follow-up of most of this population has been extended to the present. However, to obtain a sample large enough to measure the effects of relatively low-dose radiation received by organs distant from the site of primary irradiation, the program has been expanded through the collaboration of 15 population-based cancer registries. Approximately 200,000 women with cervical neoplasia are being studied. The cancer registry cohort studies have been completed, and detailed case-control studies are being conducted to provide radiation dose estimates on individuals and to evaluate dose response. Changes in serum estrogen and androgen levels, possibly associated with ovarian irradiation, are being evaluated by radioimmunoassay techniques. Chromosome aberrations in circulating lymphocytes are also being evaluated in relation to total active bone marrow dose.

2. Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhances the chances of detecting increased risks due to therapy. The study of 3,000 children treated for enlarged tonsils with radiation or surgery in Boston is nearing completion. Physical examinations have been performed on over one thousand irradiated and surgical patients in order to determine the risk of thyroid nodules more accurately and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. Blood studies include the evaluation of serum calcium levels and plasma thyroglobulin concentrations. Chromosome aberrations in circulating lymphocytes are also being investigated to assess exposure more accurately and to evaluate the effect of radiation in causing long-term damage in somatic cells from partial-body exposures.

3. A collaborative study in Israel has been completed which evaluates the risk of cancer in 10,000 children exposed to x-rays during the treatment of ringworm of the scalp and in 15,000 comparison individuals. This is a matched prospective cohort study. Malignant and benign neoplasms were ascertained by abstracting pathology records in all 22 hospitals in Israel and through record linkage with cancer and death registries. A biochemical epidemiologic study has been developed in Israel to evaluate whether the risk of thyroid neoplasms associated with a low radiation dose (9 rads) might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia

telangiectasia is a genetic disorder common among North Africans who were also found to be at highest relative risk for radiogenic thyroid disease. Cultured skin fibroblasts will be evaluated for abnormal in vitro sensitivity to ionizing radiation which would indicate an impaired ability to repair damaged DNA.

4. Over 9,000 persons who survived at least two years after a diagnosis of childhood cancer in 13 hospitals in the U.S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and matched controls to quantify the risks associated with radiation or chemotherapy treatments.

5. A population-based case-control study of thyroid cancer in Connecticut was conducted. Home interviews were completed on 159 persons who developed thyroid cancer between 1978 and 1980 and 285 controls. Radiation, diet, hormones and other risk factors were evaluated.

6. The Surveillance, Epidemiology, and End Results (SEER) and other cancer registries were used to identify second primary cancers in persons with cancers of the breast, testis, and endometrium to evaluate treatment effects and generate hypotheses about common etiologies.

7. A monograph on multiple primary cancers was prepared in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. The volume was prepared with several objectives in mind: (a) clarify the patterns of multiple primary neoplasms through systematic evaluations of all tumors developing in Connecticut and Denmark during the past 40 to 50 years, and among long-term survivors, (b) stimulate the formation of hypotheses to explain the tumor complexes and to evaluate further clinical, epidemiological or experimental approaches, (c) identify groups at especially high or even low risk of second cancer to help generate insights into carcinogenic mechanism or hose-environmental interactions, and (d) suggest strategies for future research and preventive actions.

8. New cohorts are being evaluated of women who received radiotherapy for benign gynecological disorders (BGD) in Massachusetts, New York, Rhode Island, Connecticut and Sweden. Cancers of pelvic and abdominal organs, sites which have not been well characterized in terms of radiogenic risk, are being studied. In addition, the paradoxical finding of increased leukemia risk associated with low-dose exposures to the pelvic marrow in BGD patients, but not high-dose exposures in cervical cancer patients, will be investigated, as will the unexpected reduction in breast cancer risk previously associated with irradiation for BGD in post-menopausal women.

9. The risk of leukemia in breast cancer patients treated with radiotherapy is being evaluated in a population-based case-control study in Connecticut. A total of 73 women were identified as developing leukemia at least 18 months after a breast cancer diagnosis during the period 1935-1983; two breast cancer controls have been matched to each case.

The radiation dose to the bone marrow is on the order of 2,000 rad within the radiation field (800 rad if averaged over the entire body and 70 rad outside this field). A cohort analysis of these patients using treatment data available from the Connecticut Tumor Registry suggests that women receiving radiation for their first course of treatment may have a two-fold to three-fold risk when compared to the general Connecticut population, although the possibility of missing subsequent exposure to alkylating agents could not be discounted.

10. A study of the carcinogenic effects of radiation therapy for peptic ulcer has been initiated. Over 2,000 patients who were exposed between 1937-1965 have been identified, and the radiation risks for cancers of the stomach, pancreas, lung, spleen, and kidney will be evaluated and compared with 2,500 patients treated by surgical or medical means. Except for the lung, radiation risks for these sites are not well defined.

Populations receiving diagnostic irradiation are described below.

11. A case-control study was 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. A feasibility study was successfully completed in Sweden, and a similar study of over 100,000 twins will be conducted.

12. A second mail questionnaire follow-up of women who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 was conducted to reaffirm whether repeated, relatively low radiation doses pose some future risk of breast cancer, whether the risk may be cumulative, whether adolescence is an especially sensitive age, and whether older women may be at low risk of radiogenic breast cancer. Additional studies are being conducted in Massachusetts, Connecticut, and Denmark to clarify further the carcinogenic effect of multiple low-dose x-ray exposures in both men and women.

13. Using the resources of prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, 2,000 cases of leukemia and lymphoma and 2,000 controls have been identified. Long-term histories of diagnostic x-ray exposures have been obtained for all Oakland and Portland subjects, and will soon be completed for Los Angeles subjects. The possible association of leukemia and lymphoma with radiation dose to active bone marrow will be evaluated. Radiation dosimetry has been completed, and preliminary analyses are ongoing.

14. A feasibility study of 1,645 patients treated for scoliosis at four Minneapolis-St. Paul, Minnesota, hospitals from 1935-1965 is being conducted. These patients received a large number of full spinal AP

x-ray examinations during a 3 to 5 year period in adolescence to monitor the progression of spinal curvature and treatment effects. The doses to the developing breast tissue in young girls may have been substantial enough to increase their risk of breast cancer.

Populations receiving isotopes are described below.

15. A feasibility study to extend the follow-up of patients treated with radioactive iodine for hyperthyroidism found no unusual cancer risks in patients at one large hospital in Sweden. A major expansion to evaluate the carcinogenic risks associated with diagnostic and therapeutic exposures to radioactive iodine in Sweden has been initiated. A second follow-up of patients originally identified in the National Cooperative Thyrotoxicosis Therapy Follow-up Study (TT Study) has also begun. Morbidity and mortality data are being collected on 23,000 persons treated by radioactive iodine 131-I for hyperthyroidism and 14,000 patients treated for hyperthyroidism by either surgery or anti-thyroid drugs. A feasibility study was conducted in Denmark on over 30,000 patients exposed to diagnostic doses of radioactive iodine. Radioactive iodine is an important isotope used in medicine, a major component of fallout from nuclear weapons tests, and also a major release product from nuclear power reactors. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and it is felt that further studies in this area are warranted.

16. A study that will provide a clinical evaluation of persons with nodular thyroid disease is being initiated in collaboration with Brookhaven National Laboratory (BNL). These patients were initially identified in the TT Study and received 131-I therapy for hyperthyroidism. They developed palpable thyroid nodules one or more years after 131-I treatment. These nodules, however, were not clinically evaluated by the end of the study. BNL, in collaboration with clinicians who originally participated in the TT Study, will locate these patients and invite them to return to the clinic for an examination of the thyroid gland. The final clinical diagnosis will be analyzed as a function of 131-I dose, type of hyperthyroidism, age at first treatment, and duration of follow-up to assess the risk of thyroid disease following 131-I therapy.

Other projects are intended to strengthen inferences from studies of medically-irradiated populations in general.

17. Dosimetry: An essential part of the program of epidemiologic studies of medically irradiated populations is accurate dosimetry for specific organs. A team of medical physicists has been formed to work with the Branch on dosimetry problems using physical measurements on patients, anthropomorphic phantoms, and a Monte Carlo computer code developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health, Food and Drug Administration. Radiation dose estimates for specific organs have been obtained for tuberculosis patients repeatedly exposed to fluoroscopic x-rays, cervical cancer

patients treated with intracavitary radium and external beam x-rays or gamma rays, children irradiated for enlarged tonsils, persons with leukemia who received diagnostic x-rays, patients treated with high energy accelerators that produced low levels of neutron exposures, and children treated with radiotherapy for cancer who subsequently developed a second malignancy. Determinations are ongoing for women irradiated for breast cancer, benign gynecological disorders, and endometrial cancer; men irradiated for testis cancer; persons irradiated for treatment of peptic ulcer; and persons exposed to multiple diagnostic x-rays for monitoring the progression of scoliosis.

18. Biochemical studies: The value of cytogenetic aberration data as a biological dosimeter in persons with partial-body irradiation is being explored in four medically-irradiated populations in collaboration with cytogeneticists at Oak Ridge Associated Universities. The objectives are: to determine the type and frequency of somatic cell aberrations in circulating lymphocytes in order to compare dose-response relationships with those seen in A-bomb survivors with total-body exposure; and to determine the persistence of effects in relation to sex, age at exposure, dose and dose fractionation, and radiation quality. Populations being evaluated include persons irradiated for enlarged tonsils as children, cervical cancer patients, tuberculosis patients, and persons exposed as infants for enlarged tonsils or thymic glands. Among persons irradiated for enlarged tonsils, serum tests include measurements of thyroglobulin concentrations including T3, T4, TBGI, calcium, TSH, and AMA. Cultured skin fibroblasts from several irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating perhaps an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancer.

    To evaluate an unusual lowering of breast cancer risk following ovarian irradiation for cervical cancer among premenopausal and postmenopausal women, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Currently, serum samples are being collected from 350 cervical cancer patients (175 who received radiotherapy and 175 who received surgery only) who were treated an average of 20 years ago and have been followed as part of the international radiation study of cervical cancer patients. In addition, 125 serum samples are being collected from women treated more recently (2, 5, 10 or 15 years post-treatment) as well as pre-treatment and 6-month post-treatment samples from newly diagnosed cervical cancer patients. Fifteen women who received radiotherapy and 10 women who received surgery will be evaluated for each interval group.

B. Atomic Bomb Survivors. Studies are conducted to investigate cancer risk in the survivors of the Hiroshima and Nagasaki atomic bomb explosions in order (1) to clarify the relationships between risk and radiation dose in terms of dose response, temporal distribution of risk following exposure, dependence on sex, age at exposure, and other host factors, variation by organ site and histological classification, and interactions with risk factors other than

radiation; (2) to strengthen the data base by supporting efforts to improve coverage of the tumor and tissue registries in the two cities and, through formal pathology reviews, to improve accuracy of diagnosis; and (3) to extend the value of the data base by investigating cancer risk factors other than radiation and how they interact with radiation. Investigations based on the Life-Span Study (LSS) sample of 82,000 A-bomb survivors plus 26,000 non-exposed residents are carried out at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki. The general philosophy of the program is to take advantage of the unique RERF resources to investigate interesting research questions as they arise. A typical pattern is as follows: an incidence survey for a particular cancer site is conducted using all locally available sources of diagnostic information. Attempts may be made to ascertain non-fatal cases occurring outside the two cities or, at least, to adjust risk estimates for migration. Diagnostic information is carefully reviewed, including examination of histologic materials if available, by a local investigator, either from RERF or another organization, usually a university medical school. A formal pathology review by a specially constituted panel may be performed to resolve difficult questions of diagnosis, or to provide more detailed information on histology. Statistical analyses are performed to examine questions of ascertainment bias and to estimate risk as a function of radiation dose, age at exposure, and time after exposure. A separate pathology study may be initiated to examine the possibility that precancerous lesions may be more prevalent in autopsy cases without clinical evidence of cancer. Cases and matched controls may be investigated for risk factors other than radiation exposure in a separate interview study. Because the population-based incidence study contains all the information with respect to dose response that could possibly be obtained from a case-control study based on the LSS sample, cases and controls can be matched with respect to radiation dose as well as age at exposure, city, and sex, in order to maximize statistical power for the investigation of possible interactions between radiation and other factors. Finally, once the incidence study has been completed, the A-bomb data may be combined with basic data from other irradiated populations in parallel analyses using identical strata for dose, age at exposure, and time after exposure. The LSS sample is large, has a wide dose distribution and a natural age distribution, and has been followed uniformly since 1950. Moreover, exposure occurred independently of any existing disease. Data from the LSS sample, therefore, can serve as a bridge by which inferences from other, less general, data sets can be extrapolated beyond their more restricted exposure ages, dose levels, lengths of follow-up, and circumstances of exposure.

1. An incidence study of colorectal cancer is being combined with a case-control interview study that will address occupational, dietary, exercise, and other life-style factors.

2. A feasibility study of thyroid cancer, diet, and other factors has been conducted using information already available at RERF. A thyroid cancer case-control study is under development, focusing on dietary and reproductive factors. The questionnaire was designed during a visit to NCI by the principal RERF collaborator and has undergone subsequent revision. It is now intended that the study will be extended to cases

from the general populations of Hiroshima and Nagasaki, including both A-bomb survivors and persons who were not present at the bombings, with controls drawn from RERF study populations and matched for age, sex, exposure, and radiation dose if exposed. Seven hundred cases of thyroid cancer have been identified with diagnoses during 1971-1985, of which perhaps 500 might be accessible for interview, based on past experience.

3. A survey of breast cancer incidence during 1950-1980 is essentially complete except for journal publication. This study has also been used to evaluate the influence on risk estimates of migration patterns and patterns of delayed reporting to tumor registries.

4. A case-control interview study of breast cancer cases identified in the incidence study, and multiple controls matched by city, age ATB (at the time of the bombings), and radiation dose, yielded completed interviews from 202 cases and 572 controls on 93% of those eligible. In addition, data on reproductive history, socioeconomic status, and other variables were obtained from RERF files of past studies and from mail questionnaires for many of the cases and controls. One purpose of the study was to investigate risk factors other than radiation, but the primary purpose was to examine possible interactions or synergisms between radiation and other risk or host factors in the causation of breast cancer.

5. A case-control interview study using next-of-kin informants is being used to investigate the relationship of lung cancer risk to carcinogens other than radiation, including tobacco smoke in particular, and to clarify the interactive relationship of radiation and smoking in carcinogenesis.

6. Serious attention is being given to ways in which the death certificate data, which are the mainstay of the LSS, might be improved by the routine incorporation of improved diagnostic information from tumor and tissue registries, autopsies, and clinical records. As a beginning, migration histories are being compiled for all LSS sample members, and death certificate diagnoses are being compared with diagnoses from the Hiroshima and Nagasaki tumor and tissue registries. A search of the Osaka tumor registry showed that a high proportion of recent cancer deaths among LSS sample members, identified from death certificates to have died in Osaka, are included in the registry.

7. Two new studies will use stored sera obtained during regular biennial health examinations of members of the LSS clinical subsample. In these studies, sera will be assayed and compared between persons who developed cancer after the sera had been collected, and age-sex-dose-matched controls. Assays will be of two types: cases of breast, thyroid, ovary, and prostate cancer will be compared with controls with respect to hormone levels in stored sera, including estradiol, free and bound to sex hormone binary globulin (SHBG), prolactin, DHEA-S; T_3 and T_4, thyroglobulin and anti-thyroglobulin antibody, anti-thyroid-microsomal antibody, TSH; testosterone, free and bound to SHGB, dihydroxy testosterone. Lung and stomach cancer cases and controls will be compared with respect to

the following nutrients and trace elements: retinol, alpha-tocopherol, beta-carotene, retinol binding protein, selenium, zinc, ferritin, transferrin, and ceruloplasmin. These studies are being carried out in collaboration with scientists from the Biostatistics Branch and Nagasaki University, Oxford University, and Battelle Northwest Laboratories, as well as RERF.

8. A binational pathology review of the RERF lung cancer series is being planned in collaboration with Dr. Mason of the Environmental Epidemiology Branch. This review will be accompanied by a parallel evaluation of lung cancer materials from U.S. uranium miners exposed to alpha irradiation from radon daughter products. The review, using materials collected by Dr. Vito Saccomono in Grand Junction, Colorado, will be carried out by the same binational team that reviews the RERF series. Besides providing authoritative classifications for each of the two series using a common standard, the parallel reviews should highlight differences and similarities between lung cancers induced by acute exposure to gamma rays from an external source and by protracted exposure to internal alpha emitters. Two questions of particular interest are (1) whether sensitivity to lung carcinogenesis from alpha emitters demonstrates the same decline with increasing age at exposure as that seen among A-bomb survivors, and (2) why smoking and radiation appear to interact multiplicatively in the uranium miners and additively in the A-bomb survivors. The pathological review cannot be expected to answer these questions directly but may provide histological clues to the plausibility or implausibility of various mechanistic explanations for the epidemiologic data.

9. In a collaborative study with the Clinical Epidemiology Branch, which is taking the lead role, cultured skin fibroblasts from breast cancer cases and controls are evaluated for susceptibility to cell-killing by gamma rays from a cobalt-60 source at Brookhaven National Laboratory. The purpose of this study is to see whether cancer cases are more susceptible to radiation-induced damage and, further, to see if susceptibility may be more pronounced in persons whose cancer is likely to have been induced by radiation.

10. Esophageal dysplasia and other possibly premalignant conditions are being studied, using LSS sample autopsy materials, in collaboration with Dr. M. Tokunaga, a pathologist at Kagoshima Municipal Hospital. When the pathological findings have been obtained, they will be analyzed with respect to age, radiation dose, and alcohol consumption.

C. Occupational and Environmental Exposures. The objectives of this project area are to evaluate the long-term effects of chronic exposure to radiation as a consequence of occupational or environmental exposures and to collaborate with other governmental agencies involved in radiation research. Although the possibility of increased cancer risk associated with chronic occupational exposure to low-LET radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and

largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk.

1. The existence, since 1926, of a professional registry of about 170,000 medical x-ray technologists offered a unique opportunity for studying a large and well-defined population occupationally exposed to highly fractionated low-LET radiation. Since most x-ray technologists are women, the registry provides a chance to study the two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, at the level of incidence in a population with at least some exposure at particularly vulnerable ages. Questionnaires have been sent to approximately 140,000 active members, with over 50,000 returned to date. Additionally, two-thirds of the inactive members have been located. Various tracing strategies have been undertaken to locate the remaining inactive members, as well as active members who did not respond to the questionnaries.

2. Although other governmental agencies are sponsoring large-scale investigations of occupationally exposed workers, our efforts in this area have increased with the addition in 1984 of two staff members with experience in occupational studies. A feasibility study of nuclear power workers has been developed, studies of persons occupationally exposed to uranium are being completed, tracing support for a study of Oak Ridge employees who worked on the Manhathan Projects at the K-25 plant is being provided, tracing support for a study of radium dial painters is being considered, and a study of lung cancer risk and radon exposure in the home has been initiated in Sweden which includes long-term dosimetry evaluations.

3. Radon exposure in the home has been suggested as an important risk factor for lung cancer. A large-scale case-control study, utilizing resources already available, is being considered. A Swedish study of female lung cancer patients matched to controls selected from various sources has provided a basis for testing the feasibility of obtaining track etch detector evaluations of residential radon exposures of these subjects. The track etch exposure evaluations will be extended to other study subjects, and the risk of lung cancer associated with radon will be evaluated in 200 cases and 400 controls.

4. A study of 4,101 white males occupationally exposed to uranium is being completed in collaboration with the Oak Ridge Associated Universities. This study examines the possible health effects, including cancer, observed among workers who are chronically exposed to low levels of uranium. Two studies, mortality and morbidity, are nearing completion.

5. A study of thyroid nodules associated with high natural background areas in China is being developed.

6. Branch members have also been called upon to assist in the evaluation of controversial reports, such as the studies on the effects of fallout from nuclear weapons tests in the western United States.

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. One particular approach involves reanalyses in parallel of basic data from published studies of cancer risk in different irradiated populations, in collaboration with the original authors of these 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 been initiated. The usefulness of personal computers in epidemiologic research is being evaluated.

For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an approach is being taken with respect to thyroid cancer incidence data from several exposed populations. Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of base-line and excess risk are compared, as well as integrated risk over the entire period of observation. Approximate 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 Argonne National Laboratory, the Environmental Protection Agency, the DHHS subcommittee to coordinate federal radiation activities, the Three Mile Island Public Health Advisory Group, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the World Health Organization, and two chartered NIH committees for the preparation of radioepidemiologic tables for the computation of assigned risk for cancer following radiation exposure.

F. Review Papers. Several review papers concerning health effects following exposure to ionizing radiation were written, including a review of cancer following medical irradiation, the epidemiology of radiogenic cancer of the digestive tract and other organs, the statistical aspects of estimating cancer risks from low doses of ionizing radiation, the importance of latent period, the importance of risk projection and time-response models, the long-term effects of radiation upon children, and the risk of cancer following treatment with radioactive iodine. A monograph describing the patterns over time of multiple primary cancers was prepared in collaboration with the Conneticut Tumor Registry and the Danish Cancer Registry.

G. Workshop on Women Irradiated for Benign Gynecologic Disease. A two-day workshop was sponsored by the Branch, and investigators from most of the major studies of women irradiated for benign gynecologic disease met and agreed to combine their data on mortality for over 12,000 irradiated subjects. Such data will provide important new knowledge on the risks associated with irradiation of abdominal and pelvic organs, which have not been well characterized. A summary of the workshop proceedings was submitted for publication.

Major Findings:

A. Medical Exposures.

1. The international study of 200,000 cervical cancer patients treated with radiation and/or surgery suggests that the risk of radiation-induced solid cancers may remain throughout life; exposures at young ages may carry the greatest relative risk, but exposures at both young and old ages result in high absolute risks; large doses to limited volumes of some sites, such as the rectum and bladder, may induce cancer; leukemia may be associated with non-sterilizing low doses received by bone marrow outside the pelvis; and ovarian damage caused by radiation may lower breast cancer risk, even among postmenopausal women. Thus far, preliminary cancer registry studies suggest that (1) heavily and moderately irradiated sites taken together, i.e., those likely to have received over 100 rads of radiation, show a consistent pattern of increased risk with time after exposure that is probably radiation related; (2) in particular, cancers of the bladder, rectum, bone, connective tissue, uterine corpus, ovary, small intestine, kidney, and multiple myeloma may be associated with radiation in this study; (3) the relative risk of cancers of heavily and moderately irradiated organs was greatest among those under age 30 at exposure, but generally constant among older women; (4) substantial radiation doses to the stomach, colon, liver, and gallbladder do not appear to increase risk beyond normal expectation; (5) the radiation regimens used to treat cervical cancer are not as effective in inducing leukemia as are other radiation exposures that have been studied, but a slight risk may be associated with the low-dose radiation received by bone marrow outside the pelvis; (6) radiation effects on the ovary may lower breast cancer risk at all ages of exposure, even in postmenopausal women; (7) a small excess of thyroid cancer might be associated with relatively low-dose exposure; and (8)

second cancers of other sites that received relatively low doses of radiation are either not increased beyond expectation or are probably elevated due to exposures to other strong risk factors such as cigarettes or alcohol.

2. A study of women who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis indicates that repeated relatively low radiation doses pose a long-term risk of breast cancer, that the risk may be cumulative, that adolescence is an especially sensitive age, and that older women may be at low risk for induction of radiogenic breast cancer. A new cohort of 4,174 female tuberculosis patients in Massachusetts was studied. Relative risks of 1.1 and 1.2 were computed for breast and lung cancer mortality, respectively. A modest elevation of breast cancer incidence (RR=1.4) reflects the moderate exposure which was estimated to be 66 rads per breast.

3. Children irradiated for benign conditions of the head and neck were found to be at high risk of developing thyroid neoplasia in several studies. Radiotherapy for ringworm of the scalp also increased the risk of brain malignancies, and a significant risk of leukemia was found for the first time. A study of children treated for enlarged tonsils, including physical examinations of exposed and nonexposed persons, suggests an increase of radiogenic thyroid nodules.

4. An increased risk of childhood malignancies was confirmed in twins exposed to prenatal x-ray.

5. In an international study, the cumulative 25-year risk of developing a second malignancy following treatment of childhood cancer had been found to be approximately 12%. The development of several second cancers following childhood cancer therapy, especially osteosarcomas and thyroid cancers, but not leukemia, appeared to be associated with radiation therapy. An on-going case-control analysis demonstrated a strong dose-response relationship for the induction of bone cancer following radiotherapy, but the corresponding pattern of leukemia risk by dose was flat. While sex did not appear to influence subsequent risk of developing second malignancies in these children, age at therapy did. Adolescence appeared to be a time of increased susceptibility to radiogenic osteosarcoma, possibly because of the active bone growth during this period, whereas young children appeared especially prone to radiogenic thyroid cancer.

6. Preliminary results of studies of circulating lymphocytes in persons irradiated for lymphoid hyperplasia indicate a small, but statistically significant, elevation of chromosome aberrations, i.e., translocations and inversions, among the exposed. Age and smoking status, however, appear to be important determinants of response. Results from studies of cervical cancer patients who received much larger radiation doses to the bone marrow indicate a significant four-fold increase in stable aberrations among the exposed compared to nonexposed patients.

7. A population-based case-control study of thyroid cancer in Connecticut indicated a high risk associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. No risk was found among persons diagnosed with thyroid cancer under age 35 in 1978, a finding consistent with the declining use of radiotherapy for benign conditions in the 1950s. Consumption of vegetable goitrogens appeared to decrease risk. Increasing number of live births appeared to pose a risk for women irradiated previously. Increased risk were also associated with adolescent obesity in women; multiparity, miscarriage and late age menarche among women who developed thyroid cancer before age 35; a history of benign thyroid nodules (RR=52), goiter (RR=6.6), or partial thyroidectomy; use of diuretics (RR=1.7); a history of benign breast disease (RR=2.0); and a family history of thyroid cancer (RR=3.5). About 9% of the thyroid cancers could be attributed to prior childhood head and neck irradiation.

8. A significant risk of developing a second breast cancer among 27,000 patients in Connecticut was found, and a case-control study of long-term survivors is being conducted to learn whether the increased risk might be related to a particular therapy.

9. Radiation to the pelvis for the treatment of breast cancer and also cervical cancer was associated with elevated rates of endometrial cancer.

10. Radiotherapy in combination with chemotherapy did not increase the risk of leukemia in patients with ovarian cancer, gastrointestinal cancer, or childhood cancer beyond that expected from chemotherapy alone.

11. The risk of radiogenic cancer was evaluated in over 12,000 uterine corpus cancer patients diagnosed in Connecticut during 1935-1980, with follow-up for a second primary cancer through 1982. Irradiated patients had an increased risk of developing leukemia, whereas no increased risk was seen for patients receiving surgery alone. All of the increase was attributable to patients diagnosed after 1960. Little excess was observed for digestive, bladder, and kidney cancer until 20 years after irradiation.

12. Among 1,330 men with testis cancer reported to the Connecticut Tumor Registry between 1935-1981 and followed up to 42 years, 86 developed a second cancer versus 39 expected based on general population rates. Radiotherapy and other treatments were associated with only a small proportion of the excess second cancers, suggesting that most of the risk is due to factors other than therapy and factors yet to be determined.

13. 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.

14. The risk of developing a second primary cancer was evaluated in over 250,000 persons reported to the Connecticut Tumor Registry during 1935-1982. Radiotherapy for the first cancer appeared to be responsible for the development of subsequent tumors among several groups of patients. Radiotherapy was correlated with second cancers of the rectum and other sites among cervical cancer patients and leukemia among patients with uterine corpus cancer. Bone cancers, known to be associated with high-dose radiotherapy, appear to be increased following radiotherapy for cancer of the breast, cervix, uterine corpus, connective tissue, and retinoblastoma. Cancer of the connective tissues, also known to be associated with high-dose radiotherapy, appeared to be increased following radiotherapy for ovarian cancer, bone cancer, and non-Hodgkin's lymphoma. Numerous new associations were identified, and possibilities for future study suggested.

B. Atomic Bomb Survivors.

1. The temporal patterns of risk following exposure show a striking similarity between excess risk and age-specific population rates for cancers of the breast, lung, and digestive organs consistent with the relative risk model for projection of risk forward in time.

2. Data analyses continue for case-control interview studies of breast and lung cancers. Preliminary analysis of the possible interaction between lung cancer and cigarette smoking are consistent with an additive model, as opposed to the multiplicative model seen for uranium miners.

3. A major effort was made to update the RERF breast cancer incidence series, resulting in an increase from 360 to 564 confirmed breast cancer cases, including 10 bilateral cases, diagnosed during 1950-1980. These data, which strengthened the established connection between radiation dose and breast cancer risk, are remarkable in that, for the first time, a dose-related risk appeared among women exposed before the age of 10, that is, well before breast development. The excess in this youngest cohort appears comparable to that seen in women exposed at ages 10-19, previously thought to be the ages of maximum sensitivity for radiation-induced breast cancer. As seen for older cohorts, the excess risk did not appear until ages at which breast cancer risk normally becomes appreciable. Although no excess risk was apparent for women exposed at any age after 40, there was not, as in the 1950-74 series, a dose-related deficit of breast cancer in the 40-49 ATB cohort, thus removing the motivation for an earlier interpretation that radiation to the ovaries of women of perimenopausal ages may have reduced risk by disrupting hormonal output. As in previous series, the excess risk was roughly proportional to dose, within age-ATB cohorts, but the additional number of cases provided direct evidence of an excess risk at breast tissue doses as low as 8-16 rads. Data on migration from Hiroshima and Nagasaki and on reporting delays were used to estimate the degree of underascertainment of breast cancer in the sample. An RERF technical report is in press and manuscripts are being prepared for journal submission.

4. The available histologic materials for the diagnosis of breast cancer in the LSS sample members through 1978 (essentially those in the Hiroshima and Nagasaki tumor and tissue registries, and those collected earlier for the 1950-1974 breast cancer series) were reviewed by a panel of pathologists from Japan and the United States. Three hundred cases were confirmed and classified by subtype. The review removed the possibility of future controversy about these particular cases, a matter of concern in view of some discrepancies among the three incidence series previously reported. No subtype differences were associated with radiation dose or with age at either diagnosis or exposure.

5. More than 3,000 breast tissue slides were prepared from 353 autopsy cases without clinical breast cancer, including 181 with estimated radiation doses over 50 rads, and reviewed for the existence of pre-neoplastic change. A preliminary analysis indicates that dose-related differences were stronger in the survivors exposed at younger ages. Of particular interest is the comparison for ages 40-49 and 50+ ATB, in which a statistically significant association was seen for the former cohort but not the latter. In combination with the results of the incidence survey, these results suggest a gradual decline in susceptibility to radiation carcinogenesis with increasing age at exposure.

6. Preliminary analyses of the breast cancer case-control interview study indicate that the usual reproductive factors identified in other studies are also associated with breast cancer risk in the LSS sample (e.g., RR=2.0 for first full-term pregnancy after age 30, RR=0.5 for artificial menopause). Additional analyses await a quality control procedure in which data on similar questions from different sources are compared and evaluated.

7. Interviewing has been completed for a case-control study of lung cancer focusing on smoking history, diet, and occupational history. This study involved subject or next-of-kin interviews with over 500 lung cancer cases diagnosed during 1971-1980 and age-sex-city matched controls. Preliminary analyses indicate that cigarette smoking and radiation dose are additive or subadditive in effect, contrary to the finding of multiplicativity from uranimum miner data.

8. Colon and rectal cancer is being investigated using an approach similar to that for breast cancer. Incident cases diagnosed during 1950-1982 are being ascertained and reviewed. The study has identified 386 cases of colon cancer and 343 cases of rectal cancer in the LSS sample. Preliminary analyses indicate a strong dose response for colon cancer, especially the sigmoid colon but also other segments, but none for rectal cancer. Interviews of cases and controls in Hiroshima and Nagasaki are nearly complete in a study aimed at evaluating dietary influences, occupational exposures, and physical activity as risk factors.

9. A thyroid cancer incidence study has been completed at RERF as part of its regular research program. Data from this study, and from several

other series from the United States and Israel, have been sent to NCI for comparative analyses of thyroid cancer risk as a function of radiation dose, sex, age at exposure, and time after exposure, in collaboration with the original investigators.

10. An analysis of latent periods for leukemia, and cancers of the breast, lung, and digestive system among LSS sample members shows a clear dichotomy between leukemia and the solid cancers. The frequently cited temporal "wave" phenomenon for radiation-induced leukemia appears to be real, but depends upon histologic type and age at exposure. There is also much less reason to suspect a dependence of induction period on radiation dose for radiation-induced leukemias. The temporal pattern for leukemia is in marked contrast to cancers of the breast, lung, and digestive organs, for which the distribution in time of radiation-induced cancers appears similar to that for non-radiation-induced cancers, for subjects of the same age ATB. It seems that radiation exposure increases cancer risk, but that the additional cancers appear at ages when cancers normally occur, and are distributed over time as one might expect on the basis of age-specific population rates.

C. Occupational and Environmental Exposures.

1. Cancer risk is being evaluated among more than 170,000 x-ray technologists registered since 1926 with the American Registry of Radiologic Technologists. Optical scan questionnaires were sent to approximately 144,000 active members with known addresses. To date, over 50,000 questionnaires have been returned. About 20,000 of the 30,000 inactive members of the registry have been located. Various methods are being employed to increase the response rate. Preliminary findings suggest a higher than expected incidence of thyroid cancer among this group.

2. A re-evaluation of geographic and temporal mortality among residents of southwestern Utah failed to confirm a previously reported study of excess cancers among Mormon residents in that area during the period and potentially exposed to radioactive fallout from nuclear weapons tests. On the other hand, an evaluation of leukemia mortality, while failing to substantiate claims of greatly increased cancer risk, obtained results consistent with an increase in leukemia mortality among children during the period 1955-1971 who were born before 1958.

D. Methodologic Studies.

1. Because assumptions about dose response are needed to estimate cancer risks associated with low-dose exposures, and because these assumptions should be based on radiobiological considerations, the Branch has encouraged contacts between staff members and experimental radiobiologists to the extent of participating in analyses of experimental data. One such study is a long-term animal experiment in rats to assess possible interactions between radiation and other carcinogens for the

induction of mammary tumors. The experimental design was a 2^3 factorial with tumor incidence determined by palpation and biopsy over a two-year period followed by necropsy. The unusual analytic problems presented by this design were addressed by an adaptation of the proportional hazards model.

2. The incorporation of prior information about details of the dose-response model is subject to criticism on grounds of arbitrariness. Uncertainties about model choices should be reflected in the estimates obtained, and the estimation process should be subject to the discipline of a coherent system of inference. A Bayesian approach satisfies these conditions and, moreover, results in estimates suitable for the application of optimal decision rules.

3. 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.

4. Breast cancer risk among A-bomb survivors has been explored using new models in which the magnitude of risk and its distribution over time are treated simultaneously with age at exposure. The analysis suggests that the magnitude of risk and its temporal distribution are essentially independent, but that both are heavily dependent upon age at exposure. This result confirms previous analyses which treated questions of magnitude and temporal distribution orthogonally and separately, rather than simultaneously.

5. To develop more efficient techniques and resources to locate persons exposed to carcinogens in the past, several new initiatives have continued. In collaboration with the Environmental Epidemiology Branch, tracing firms have been issued Master Agreement Orders to compete for specific task order Requests for Proposals in order to trace persons using credit bureaus, motor vehicle departments, city and public directories, vital statistics departments, and special individual techniques. Additional sources that have been used include the Social Security Administration, the Health Care Finance Administration, the Veterans Administration, the Internal Revenue Service, the U.S. Post Office, the National Death Index (NDI), and various state mortality files. To extend state mortality coverage retrospectively prior to 1979 when the NDI began, meetings and negotiations have been held with several state and national committees.

6. To utilize the resources of population-based cancer registries, record linkage master agreements have been made with more than 20 cancer registries in the U.S. and other countries. This resource will be used to evaluate effects of treatment, occupation, and other factors in cancer etiology. Record linkage studies have been conducted successfully in several registries in the U.S. and around the world, e.g., second cancers following cervical cancer in 15 registries; childhood cancers in twins in

Connecticut and Sweden; cancer after radioactive iodine exposure in Sweden; and a variety of second cancer studies in Connecticut and other SEER registries.

Significance to Biomedical Research and the Program of the Institute:

Studies of populations exposed to ionizing radiation are conducted to investigate further the relationship between cancer risk and exposure to high doses and to improve estimates of risk associated with lower doses. An immediate practical need is for risk estimates on which to base decisions about the use of nuclear and radiological technology in medicine and industry. Epidemiologic data relating cancer incidence and mortality to radiation exposure, especially with good information on dose and timing of exposure, can also influence theories of carcinogenesis and motivate experimental research. In many exposed populations, quantitative and qualitative descriptions of exposure to affected tissues are straightforward, an advantage not available for most other carcinogens; furthermore, epidemiologic studies can draw upon the background of a vast literature of experimental and theoretical radiobiology, including radiation carcinogenesis in experimental animals, as well as studies at the cellular and subcellular levels.

The importance of radiation studies for understanding carcinogenesis is illustrated by a series of breast cancer incidence studies carried out by the Radiation Epidemiology Branch. With remarkable consistency, these studies indicate (1) that sensitivity to radiation carcinogenesis can be heavily dependent on developmental factors but relatively independent of factors responsible for international differences in population rates, (2) that there may be wide variations among tissues with respect to the form of the dose-response curve, and (3) that while there is a recognizable "wave" in time of excess leukemia risk following radiation exposure, for many other radiation-induced cancers the time from exposure to diagnosis simply reflects age-specific population rates--that is, risk is increased, but the timing of that risk is unaffected by radiation dose.

Proposed Course:

Activities will continue in all four project areas involving radiation studies. The aim is to assure that maximum benefit is derived from existing epidemiologic resources and to initiate studies of populations not previously evaluated, but which offer unusual potential for new information. Populations that have been identified in the past will be followed continually in order to evaluate lifetime risks associated with previous exposures. The extent of the follow-up will vary, depending upon the particular population being evaluated, but could include mail questionnaire studies, National Death Index searches and other mortality evaluations, or record linkage with existing regional tumor registries. Populations designated for future follow-up include (1) the atomic bomb survivors, (2) tuberculosis patients in Massachusetts and Connecticut who received multiple chest fluoroscopies, (3) women given radiotherapy for cervical cancer, (4) children irradiated for lymphoid hyperplasia, (5) x-ray technologists, (6) women given radiotherapy for benign

gynecologic disorders (BGD), (7) patients treated for hyperthroidism by radioactive iodine, and (8) children treated for retinoblastoma. The latter three studies were recently initiated. For the study of BGD, cancers of pelvic and abdominal organs, sites which have not been well characterized in terms of radiogenic risk, will be evaluated. In addition, the paradoxical finding of increased leukemia risk associated with low-dose exposures to the pelvic marrow in BGD patients, but not with high-dose exposures in cervical cancer patients, will be investigated, as will the unexpected reduction in breast cancer risks previously associated with radiotherapy for BGD in postmenopausal women.

New studies that are in the planning or feasibility stage include:

(1) An evaluation of persons with scoliosis who received multiple diagnostic x-rays of the spine during adolescence. Such a study would prove valuable in evaluating the risk of breast cancer from repeated low-dose diagnostic x-ray exposures received during an especially sensitive time of life.

(2) To quantify and clarify the findings of an increased risk associated with prenatal x-ray exposure in twins in Connecticut, an expanded study utilizing twin registries and cancer registries in California and Sweden was considered. The pilot effort in Sweden demonstrated the feasibility of obtaining the information required to support a full-scale study and provided the basis for the development of a definitive study plan. Funding for this research has been approved and the work is to begin shortly. About 100 cases of childhood cancer and 200 comparison subjects will be compared for prenatal x-ray exposure while covariables relevant to childhood cancer incidence will be controlled.

(3) A case-control evaluation of the risk of contralateral breast cancer in women treated with radiation for primary breast cancer has been initiated in Connecticut and in Denmark. The dose to the contralateral breast can be substantial, on the order of several hundred rads, and survival following breast cancer treatment is relatively good. Thus, this study offers an opportunity to evaluate the risks of radiation in older women and the effect of interaction of radiation with an underlying host susceptibility.

(4) There has been wide interest in evaluating health effects in U.S. nuclear power workers. Because of the magnitude of such an investigation, coupled with the long-term commitment required, we have been cautious in embarking on such a project. A feasibility study, however, has been developed, and permission to conduct the feasibility effort has been obtained from the medical and management staff of one nuclear power station.

(5) Radon in the home has been suggested as an important risk factor for lung cancer. A study in collaboration with the Environmental Epidemiology Branch is being considered, as is an extension of an ongoing case-control study of lung cancer in women in relation to passive smoking and radon exposure, for which enhanced dosimetric evaluations are being planned. A collaborative study in Stockholm has been initiated to evaluate the risk of lung cancer and

radon exposure among female residents who would be less likely than males to smoke and who would be more likely to spend significant amounts of time in their homes.

Other studies under consideration include:

(1) Populations exposed to non-ionizing radiation are being considered for potential study. For example, recent reports in the literature suggest an association between leukemia and electromagnetic radiation.

(2) The ability of neutrons to induce cancer in humans has not been well-studied, and a study of patients who received neutron exposure from betatrons and other high-energy cancer therapy machines or neutron sources would provide new information.

(3) The study of chromosome aberrations following radiation exposure may be extended to other populations, such as cancer patients who were treated with neutrons or cytotoxic drugs.

(4) A study of the possible association between high natural background radiation and thyroid nodules is being considered in China, and discussions with collaborating agencies have begun.

(5) A population-based case-control study in Connecticut is being developed to quantify the risk of second cancers following treatment for endometrial cancer. The peculiar excess of leukemia observed in the cohort evaluations, which has not seen for cervical cancer, will be evaluated.

(6) A study is being considered, in collaboration with the Biometry Branch, of children, adolescents, and young adults who developed cancer to determine their risk of developing a second primary cancer. Two cohorts would be examined: (1) 1,953 children and 6,298 young adults from the Connecticut Tumor Registry, diagnosed between 1960-1980, and (2) 4,558 children and 19,636 young adults from the SEER registries, diagnosed between 1973-1980, including Connecticut.

(7) A study of hormone profiles in women irradiated for benign gynecologic disorders (BGD) is proposed. A deficit of breast cancer after radiotherapy for BGD has been reported in several populations. One study found a lower risk of breast cancer for women who where irradiated after menopause. The proposed study would provide an opportunity to evaluate hormone profiles in women who received lower ovarian radiation doses and compare them to cervical cancer patients who are currently being evaluated.

(8) A follow-up of some 1,800 children treated for retinoblastoma in New York and Massachusetts as early as 1919 is being considered. Very high rates of second cancers have been reported previously, most notably for osteosarcomas. This investigation would be in collaboration with the Clinical Epidemiology Branch.

The collaborative program of A-bomb survivors studies, using data resources of the Radiation Effects Research Foundation, will continue to be focused primarily on site-specific studies of cancer incidence and radiation dose, and case-control interview studies of factors other than radiation, both alone and in combination with radiation. Where appropriate, as with thyroid cancer for which risk factors other than radiation are poorly understood, the case-control approach may be extended to the general population covered by the Hiroshima and Nagasaki tumor and tissue registries, including persons who are neither A-bomb survivors nor members of the LSS sample. Exploration will continue for ways to utilize cancer risk and exposure data on A-bomb survivors not included in the LSS sample. For example, studies of fairly infrequent cancers may be amenable to a case-control approach, based on sampling from various identified cohorts of survivors other than the LSS sample.

Efforts will continue to make use of case-finding resources to improve the ascertainment of cancer morbidity among members of the LSS sample who no longer reside in Hiroshima or Nagasaki. A national registry of thyroid cancer, for example, is said to cover 85% of all currently diagnosed cases in Japan. Data from clinical, pathology, and laboratory sources (such as stored sera) will be increasingly sought for incorporation into epidemiologic studies of survivors. This will include designing studies, recruiting specialist collaborators, and providing financial support for technical requirements, as appropriate. Where possible, such studies will be done to facilitate comparison with similar studies of other populations, including the incorporation of materials from other populations into the ascertainment process.

The epidemiology of radiation carcinogenesis is concerned with questions that go far beyond the identification of radiation as a cancer risk factor for certain tissues. In particular, estimates of cancer risk from low-dose exposures to low-LET radiation must eventually depend on epidemiologic data obtained at higher dose levels. However, elucidation of the nature of that dependence probably will come from other radiobiological considerations, including the results of studies of experimental carcinogenesis, microdosimetry, and radiation effects such as chromosomal abnormalities, that, unlike cancer, can be easily studied at low doses. Therefore, the development of statistical and epidemiologic expertise in the area of radiation carcinogenesis depends to a large extent on closer association between persons involved in epidemiologic, experimental, and theoretical approaches to the problem. Another likely benefit of such association would be to encourage experimental investigations of questions arising from epidemiologic studies, such as the relative sensitivities to radiation carcinogenesis of pre- and postpubertal, and pre- and postmenopausal breast tissue. For these reasons, increased collaborative research is planned involving experimental radiobiologists at the Brookhaven and Oak Ridge National Laboratories and elsewhere, such as the current study of chromosome aberration frequencies in three exposed populations also under study for cancer risk, and possible reanalyses of experimental dose-response data by project members.

Publications:

Boice, J. D., Jr., Beebe, G. W. and Land, C. E.: Absolute and relative time-response models in radiation risk estimation. In Some Issues Important in Developing Basic Radiation Protection Recommendations. Washington, D. C., National Council on Radiation Protection and Measurements, 1985, pp. 22-50.

Boice, J. D., Jr., Day, N. E., Andersen, A., Brinton, L. A., Brown, P., Choi, N. W., Clarke, E. A., Coleman, M. P., Curtis, R. E., Flannery, J. T., Hakama, M., Hakulinen, T., Howe, G. R., Jensen, O. M., Kleinerman, R. A., et al.: Second cancers following radiation treatment for cervical cancer: An international collaboration among cancer registries. JNCI 74: 955-975, 1985.

Boice, J. D., Jr. and Fraumeni, J. F., Jr.: Second cancer following cancer of the respiratory system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Boice, J. D., Jr., Storm, H. H., Curtis, R. E., Jensen, O. M., Kleinerman, R. A., Jensen, H. S., Fraumeni, J. F., Jr. and Flannery, J. T. (Eds.): Multiple Primary Cancers in Connecticut and Denmark. Natl. Cancer Inst. Monogr. (In Press)

Crawford-Brown, D. and Wilson, J.: Observations on very long-term removal of uranium compounds. Health Phys. 47: 443-446, 1984.

Curtis, R. E., Boice, J. D., Jr., Kleinerman, R. A. and Fraumeni, J. F., Jr.: Multiple primary cancer in Connecticut, 1935-1982. Natl. Cancer Inst. Monogr. (In Press)

Curtis, R. E., Hoover, R., Kleinerman, R. A. and Harvey, E. B.: Second cancer following cancer of the female genital system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Ewertz, M., Machado, S. G., Boice, J. D., Jr. and Jensen, O. M.: Endometrial cancer following treatment for breast cancer: A case-control study in Denmark. Br. J. Cancer 50: 687-692, 1984.

Greene, M. H. and Wilson, J.: Second cancer following lymphatic and hematopoietic cancers in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Harvey, E. B., Boice, J. D., Jr., Honeyman, J. and Flannery, J. T.: Prenatal x-ray exposure and childhood cancer in twins. N. Engl. J. Med. 312: 542-545, 1985.

Harvey, E. B. and Brinton, L. A.: Second cancer following cancer of the breast in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Hoar, S. K., Wilson, J., Blot, W. J., McLaughlin, J. K., Winn, D. and Kantor, A. F.: Second cancer following cancer of the digestive system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Hoffman, D. A. and Radford, E. P.: A Review of the Carcinogenic Effects of Low Doses of Ionizing Radiation. Philadelphia, Three Mile Island Public Health Fund, 1985, 180 pp.

Hrubec, Z., Floderus-Myrhed, B., deFaire, U. and Sarna, S.: Familial factors in mortality with control of epidemiologic covaribles. Swedish twins born 1886-1925. Acta Genet. Med. Gemellol. 33: 403-412, 1984.

Kleinerman, R. A., Liebermann, J. V. and Li, F. P.: Second cancer following cancer of the male genital system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Land, C. E.: Carcinogenic effects of radiation on the human digestive tract and other organs. In Upton, A. C., Albert, R. E., Burns, F. and Shore, R. E. (Eds.): Radiation Carcinogenesis. New York, Elsevier/North-Holland. (In Press)

Land, C. E.: Estimating cancer risk from low doses of ionizing radiation. In Fritz-Neggli, H. (Ed.): Proceedings of the 18th Annual Meeting of the European Society for Radiation Biology. Zurich, September 1984. (In Press)

Land, C. E.: Extrapolation from large-scale radiation exposures: Cancer. In Shellabarger, C. and Woodhead A. (Eds.): Proceedings of Symposium on Assessment of Risk from Low-Level Exposure to Radiation and Chemicals: A Critical Overview. Brookhaven National Laboratory, May 20-24, 1984. (In Press)

Land, C. E.: Induction periods for radiation-induced cancer. J. Chronic Dis. (In Press)

Land, C. E.: Influences of Experimental and Theoretical Radiobiology on the Epidemiology of Radiation Carcinogenesis. In Gordis, L. (Ed.): Epidemiology and Risk Assessment Symposium Proceedings. (In Press)

Machado, S. G. and Bailey, K. R.: Assessment of interaction between carcinogens in long-term factorially designed animal experiments. Biometrics. (In Press)

Miller, R. W. and Boice, J. D., Jr.: Radiogenic cancer after prenatal or childhood exposure. In Upton, A. C., Albert, R. E., Burns, F. and Shore, R. E. (Eds.): Radiation Carcinogenesis. New York, Elsevier/North-Holland. (In Press)

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

Storm, H. H. and Boice, J. D., Jr.: Leukemia after cervical cancer irradiation in Denmark. Int. J. Epidemiol. (In Press)

Tokunaga, M., Land, C. E., Yamamoto, T., Asano, M., Tokuoka, S., Ezaki, H., Nishimori, I. and Fujikura, T.: Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1980. Radiation Effects Research Foundation Technical Report. (In Press)

Tokunaga, M., Tokuoka, S. and Land, C. E.: Breast. Gann. (In Press)

Tokuoka, S., Asano, M., Yamamoto, T., Tokunga, M., Sakamoto, G., Hartman, W. H., Hutter, R. V. P., Henson, D. E. and Land, C. E.: Histological review of breast cancer cases in survivors of atomic bombs in Hiroshima and Nagasaki, Japan, by Japan-U.S. pathologists. Cancer 54: 849-854, 1984.

Tucker, M. A., Boice, J. D., Jr. and Hoffman, D. A.: Second cancer following cutaneous melanoma, and cancers of the brain, thyroid, connective tissue, bone and eye in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

CONTRACTS IN SUPPORT OF THIS PROJECT

ENERGY, DEPARTMENT OF (Y01-CP-10504)

Title: Studies on Radiation-Induced Chromosome Damage in Humans

Current Annual Level: $150,000

Man Years: 1.5

Objectives: To study radiation-induced chromosome damage in four different human populations, irradiated from 15 to 50 years ago. All four populations received partial-body exposures from diagnostic or therapeutic radiation. The project was undertaken to determine the type and frequency of chromosome aberrations in circulating lymphocytes and to compare dose-response curves among these four populations with respect to dose, quality of radiation, fractionation, age, and sex. The purpose is (1) to improve the usefulness of chromosome aberration frequency as a biological dosimeter for partial-body exposures, (2) to determine the persistence of radiation-induced somatic effects, and (3) to obtain insights into a biological effect that may be similar to radiation carcinogenesis.

Methods Employed: Chromosomal aberrations are being determined and analyzed in 600 subjects selected from among four populations exposed to partial-body diagnostic and therapeutic radiation during the period 1930-1970, which are currently under study by the Branch for late health effects in relation to individual dosimetry. These populations are cervical cancer patients given radiotherapy, tuberculosis patients given multiple chest fluoroscopies, persons irradiated for lymphoid hyperplasia during childhood, and persons irradiated for enlarged thymus glands during infancy. About 50 non-exposed persons from each of these populations are selected as controls. Blood specimens, drawn at the hospitals where these persons were treated, are analyzed at the DOE-supported radiation cytogenetic laboratory at the Oak Ridge Associated Universities.

Major Contributions: To date, cultured blood samples (200 cells each) have been completed on 165 tonsil patients, 164 cervical cancer patients, 150 tuberculosis patients, and 200 patients treated as children for enlarged thymus glands. Further analyses now indicate a small, but statistically significant, difference in the frequency of chromosome aberrations in exposed persons as compared with non-exposed persons treated during childhood for enlarged tonsils. Age, sex, and smoking histories were controlled in the analysis. An increase of radiation-induced lesions was apparent for cervical cancer patients. Approximately 5 to 10 lesions per 100 cells in exposed cervical cancer patients were seen as compared with one lesion per 100 cells in non-exposed cervical cancer patients. Four-fold and five-fold differences were found for inversions and translocations, respectively, in irradiated versus non-irradiated patients. Dicentrics and rings were not increased in exposed patients.

Proposed Course: The study is planned to be extended to other populations which have received radiation at different exposure levels and at different ages. Comparisons with atomic bomb survivor data are planned. There is a unique opportunity to draw and analyze blood from cervical cancer patients who were treated with very high energy x-ray beams that produced a measurable amount of neutrons. Cervical cancer patients treated in the past at different times (i.e., 6 months, 1 year, 5 years, 10 years, and 15 years ago) will be evaluated. Women irradiated for benign gynecologic disorders will also be evaluated. Bone marrow doses in these patients have been determined to be 70-90 rad, and a two-fold leukemia risk has been reported. Thus, data on chromosomal lesions should provide an interesting contrast to the cervical cancer patients. It also may be possible to use this approach to study patients treated with neutrons and also patients treated with cytotoxic drugs. A three year extension has been approved.

TEXAS, UNIVERSITY OF, M.D. ANDERSON HOSPITAL (NO1-CP-01047)

Title: Studies of Iatrogenic Cancer and Radiation Dosimetry

Current Annual Level: $109,892

Man Years: 2.0

Objectives: To provide radiation dosimetry necessary to estimate organ doses received during exposure to either therapeutic or diagnostic radiation.

Methods Employed: Physics measurements are being made for x-ray machines and intracavitary isotopes. These include orthovoltage, betatron, megavoltage x-ray machines, Van de Graaff machines, and cobalt-60 units, in addition to radium and cesium intracavitary sources. Abstracted dosimetry data from all collaborating centers are further evaluated and organ-specific doses estimated, either by measurement, computer simulation, or literature review.

Major Contributions: The contractor has developed and refined a measurement program to obtain organ-specific doses following treatment for cervical cancer. Calculations of active bone marrow dose and measurements have been performed and compared with the results from a Monte Carlo computer technique for a mathematically described anthropomorphic phantom. Organ doses for 15,000 cervical cancer patients have been determined. Organ dosimetry has also been provided for studies of cancer following childhood cancer treatment with radiation, leukemia and lymphoma following diagnostic x-ray procedures, cancer following treatment for testicular cancer, contralateral breast cancer following radiotherapy for an initial breast tumor, and cancer following radiotherapy for benign gynecologic disorders.

Proposed Course: To complete the dosimetry determinations of women identified from all hospitals and cancer registries collaborating in the European segment of the international study of cervical cancer and to apply the developed dosimetry to other groups of women similarly irradiated for benign gynecologic

disorders. A five year extension has also been approved to provide dosimetry support for epidemiologic studies of the following populations: women irradiated for breast cancer, adolescents receiving diagnostic spinal x-rays for scoliosis, and children irradiated for lymphoid hyperplasia.

WESTAT, INC. (NO1-CP-31035)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $1,225,079

Man Years: 8.0

Objectives: To obtain technical (nonprofessional), managerial, and clerical support for epidemiologic studies. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection forms; (2) preparing manuals for abstracting, coding, interviewing, and tracing; (3) tracing individuals to determine their vital status; (4) obtaining their consent to be interviewed; (5) interviewing or sending mail questionnaires; (6) obtaining death certificates; (7) abstracting, keying, editing, updating, and coding of data; (8) occasionally transporting biological specimens; (9) assessing exposure information; and (10) creating and manipulating data files.

Major Contributions: The contractor has provided support services for the following studies: (1) the follow-up study of cervical cancer patients treated in U.S. clinics; (2) case-control studies within U.S. cancer registries for the cervical cancer study; (3) questionnaire preparation and tracing for the x-ray technologist study; (4) leukemia case-control study among breast cancer patients reported to the Connecticut Tumor Registry; (5) Veterans Administration adjuvant drug study evaluations; (6) clinical trial evaluations of leukemia risk following breast cancer; (7) follow-up and tracing for the TB-fluoroscopy breast cancer studies in Massachusetts and Connecticut; (8) study of cancer following radiotherapy for infertility in New York; (9) study of second breast cancer following radiation therapy in Connecticut; (10) case-control study of the risk of second malignancies following treatment for testis cancer; (11) cohort study of 3,000 children with lymphoid hyperplasia who were treated with and without radiation in Boston; (12) study of childhood cancer following prenatal x-ray in Connecticut and California; (13) feasibility study of nuclear power workers; (14) study of new cancers following treatment for retinoblastoma; (15) hormonal and chromosomal studies of cervical cancer patients; and (16) the Connecticut-Denmark monograph on multiple primary cancers.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-31036)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $224,618

Man-Years: 3.2

Objectives: To obtain technical (nonprofessional) managerial, and clerical support for epidemiologic studies on populations exposed to ionizing radiation, with primary focus on persons with scoliosis who received multiple diagnostic x-ray exposures of the spine during adolescence. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection instruments (medical abstract forms, questionnaires); (2) preparing training manuals for abstracting, coding, data editing, interviewing, and tracing; (3) tracing individuals to ascertain their vital status; (4) interviewing or sending mail questionnaires; (5) obtaining death certificates; (6) abstracting, coding, keying, editing, and updating of data; (7) assessing exposure information for purposes of radiation dosimetry; and (8) creating and manipulating data files.

Major Contributions: To date, one study has been supported by this contract--a retrospective cohort study of cancer morbidity and mortality among scoliotics exposed to multiple diagnostic x-ray examinations during childhood and adolescence. The feasibility study is expected to be completed by December, 1985. Current progress includes: (1) completion of medical record abstracting; (2) initiation of patient tracing; to date, over 40% of the cohort has been located; (3) initiating a mail questionnaire survey; and (4) recall of patients for a clinical examination has begun.

Proposed Course: Completion of feasibility study with expansion evaluation planned for fall of 1985.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-41018)

Title: Support Services for a Follow-up Study of Patients Treated for Hyperthyroidism

Current Annual Level: $209,499

Man Years: 3.3

Objectives: To obtain technical, managerial, and clerical support for a nationwide follow-up study of patients treated for hyperthyroidism. The contractor will also serve as the Coordinating Center for the study to insure consistent data collection techniques in the regions (New York, Boston, California, and "other") included in the study. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection instruments; (2) preparing training manuals for abstracting, coding, data editing, and tracing; (3) tracing individuals to determine vital status; (4) obtaining death certificates; (5) verifying cause of death; (6) abstracting, coding, keying, editing, and updating of data; and (7) creating and manipulating data files.

Major Contributions: To date, the principal accomplishments of the contractor in the role of Coordinating Center include: (1) the development of draft medical record abstract and locator forms to be used in all study regions; (2) the preparation of data tapes for record-linkage with the National Death Index and the Health Care Financing Administration; and (3) assisting with patient identification efforts in the California region. As area center contractor for the clinics in the "other U.S. hospitals" (University of Cincinnati, Cleveland University Hospital, Cleveland Metropolitan General Hospital, Mayo Clinic, University of Michigan, and University of Maryland), the following tasks have been completed: (1) a meeting was held with collaborators at each of these clinics and the study protocol was submitted for approval to each clinic's Institutional Review Board; (2) the draft medical abstract form is being pre-tested at each clinic; and (3) the identification of original patient rosters is continuing.

Proposed Course: Continuation of patient roster identification, medical records abstraction, and mortality follow-up is planned through 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05368-02 REB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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:	M. H. Greene	Clinical Investigator	EEB	NCI
	M. A. Tucker	Clinical Investigator	EEB	NCI
	R. E. Curtis	Statistician	REB	NCI
	R. A. Kleinerman	Epidemiologist	REB	NCI
	D. A. Hoffman	Epidemiologist	REB	NCI
	L. A. Brinton	Epidemiologist	EEB	NCI

COOPERATING UNITS *(if any)*
Danish Cancer Registry (M. Ewertz)

LAB/BRANCH
Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☒ (a2) Interviews

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

The purpose of this project is to study the long-term health effects of drugs, especially therapeutic agents, as they may relate to carcinogenicity. In addition, the patterns of occurrence of multiple primary cancer are evaluated in terms of implications for etiologic research. Because many studies of radiation carcinogenesis involve the evaluation of second cancers following radiotherapy for a primary cancer, it is often convenient to evaluate simultaneously the effects of chemotherapeutic agents. Populations studied include patients treated in randomized clinical trials, patients reported to cancer registries in the United States and other countries, and patients treated at several large institutions. Additional details can be found in Project No. Z01CP04412-09 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-09 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. Evaluations have been made on the effects of estrogens, tranquilizers, thyroid hormones, and anti-tuberculosis drugs on subsequent risk of cancer.

A study of patients given methyl-CCNU as adjuvant therapy for gastrointestinal cancer provided the first quantitative dose-response evidence that nitrosoureas are leukemogenic in man. Alkylating agents to treat childhood cancer were associated with an increased risk of leukemia. Women with breast cancer who received chemotherapy may be at an increased risk of leukemia. Women with breast cancer who received estrogen therapy were found to have an enhanced risk of endometrial cancer. Recent concerns about the possible tumor promoting effects of thyroid supplements on breast cancer risk were not substantiated. Commonly used drugs were not found to be related to thyroid cancer, although a positive association was suggested for diuretic use.

PROJECT DESCRIPTION

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

John D. Boice, Jr.	Chief	REB	NCI
Mark H. Greene	Clinical Investigator	EEB	NCI
Margaret A. Tucker	Clinical Investigator	EEB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Daniel A. Hoffman	Epidemiologist	REB	NCI
Elizabeth B. Harvey	Staff Fellow	REB	NCI
Louise A. Brinton	Epidemiologist	EEB	NCI
Robert N. Hoover	Chief, Environmental Epidemiology Branch	EEB	NCI
Joseph F. Fraumeni, Jr.	Associate Director	E&B	NCI
John Y. Killen	Clinical Investigator	DCT	NCI

Objectives:

(1) To clarify the magnitude and determinants of risk of second cancers after chemotherapy. (2) To study the long-term effects of selected drugs in humans, and to characterize risk in terms of dose and latent period as well as the influence of age, sex and race. (3) To evaluate the causes of multiple primary cancers.

Methods Employed:

1. The risk of leukemia associated with the first course of cancer treatment was evaluated in more than 400,000 cancer patients diagnosed during 1973-1980 from the Surveillance, Epidemiology, and End Results Program (SEER). The risk in 78,000 breast cancer patients treated between 1973-1982 was further evaluated.

2. A case-control study in four U.S. cancer registries and in Denmark has been completed. 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.

3. A systematic evaluation of adjuvant drug therapy for cancer treatment has continued (see also, Project No. Z01CE04412-08 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CE04410-08 EEB, "Studies of Persons at High Risk of Cancer"). To evaluate the potential carcinogenic effects of various modalities in the treatment of cancer, information from several NCI-supported cancer treatment protocols is being combined and analyzed. The program of studies is being done in collaboration with the Division of Cancer Treatment. From a survey of NCI-funded protocols,

a number of cancer treatment trials were selected for evaluation. Protocol chairmen and statisticians were contacted, available data evaluated, and abstract forms designed to obtain information on second cancers not readily available from computerized data. Collaboration has been obtained from the following surgical adjuvant groups: the Gynecologic Oncology Group, the Veterans Administration Surgical Oncology Group, the Eastern Cooperative Oncology Group, the Gastrointestinal Tumor Studies Group, the Brain Tumor Study Group, and the Southwest Oncology Group. Several large individual institutions (e.g., M. D. Anderson Hospital, Mayo Clinic, Roswell Park Memorial Institute, and Princess Margaret Hospital) are also collaborating in these studies. Drugs being evaluated include: thioTEPA, melphalan, methyl-CCNU, BCNU, cytoxan, chlorambucil, 5-fluorouracil, nitrogen mustard, and others.

4. The risk of acute non-lymphocytic leukemia (ANLL), acute myelodysplastic syndrome, and preleukemia was evaluated among 3,600 patients with gastrointestinal cancer treated in nine randomized trials. The exposure of interest was methyl-CCNU, a nitrosourea alkylating agent. Dose-response evaluations in terms of milligrams per body surface area are continuing.

5. A follow-up study of 2,600 one-year survivors of ovarian cancer in two large hospitals is being analyzed. Two special features of this new survey are (a) the availability of complete therapy dose data on every drug received by each patient and (b) an opportunity to compare directly the leukemogenic effects of melphalan, chlorambucil, and cyclophosphamide (cytoxan).

6. A study has been completed to evaluate the toxicity of nitrosourea compounds among 2,200 brain cancer patients treated in six clinical trials conducted by the Brain Tumor Study Group. One thousand five hundred patients received a nitrosourea drug, of which 85% was BCNU.

7. 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.

8. A population-based case-control study is being conducted using the resources of the SEER registries to evaluate the risk of acute non-lymphocytic leukemia in breast cancer patients treated with adjuvant chemotherapy. A feasibility study is currently underway in Connecticut to abstract complete treatment details from hospital and physician medical records for cases and controls.

9. The risk of leukemia is being evaluated among patients treated with adjuvant chemotherapy during the conduct of two early clinical trials of breast cancer. Other cooperative groups in the United States and Denmark have been contacted to extend these investigations.

10. Using the resources of the Veterans Administration clinical trials system, evaluation is ongoing of patients with colorectal cancer or lung cancer who received nitrogen mustard, cytoxan, methotrexate, or CCNU.

11. A mortality study of men and women treated with isoniazid for pulmonary tuberculosis in Connecticut and Massachusetts is continuing. Medical records and mail questionnaires were used to ascertain drug exposure.

12. A feasibility study is being conducted of epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs to evaluate possible carcinogenicity, particularly in offspring exposed in utero. Cancer registry records in Denmark are being linked with hospital lists to ascertain cancers.

13. Risk factors for thyroid cancer were investigated in a population-based case-control study in Connecticut. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978-1980 and on 285 controls. Detailed histories of commonly used drugs were taken.

14. The risk of developing a second malignancy among 1,330 men with testis cancer was evaluated using resources of the Connecticut Tumor Registry.

15. A joint monograph on multiple primary cancers is nearing completion using the resources of the Connecticut Tumor Registry and the Danish Cancer Registry (NCI Monograph No. 67). The risk of developing a second primary cancer was evaluated in over 250,000 cancer patients from Connecticut (1935-1982) and approximately 380,000 patients from Denmark (1943-1980). These data are particularly valuable in determining the risk of multiple primary cancers among persons followed for very long periods, in some cases as long as 40 years. Tabulations are included by registry, initial cancer site, second primary cancer site, sex, time interval between cancers, and, where appropriate, by age and by treatment with or without radiation. For each site, the results are summarized, compared to previously published findings, and discussed in terms of implications for etiologic research.

Major Findings:

1. Analysis of data from the follow-up study of patients with gastrointestinal cancer showed that those given methyl-CCNU as adjuvant therapy were at a 16-fold excess risk of developing leukemia. This study provided the first quantitative evidence that nitrosoureas are leukemogenic in man, and confirms previous observations that adjuvant chemotherapy with alkylating agents may increase the risk of leukemia. Preliminary analysis of dose information suggest a significant increase in risk with increasing dose per body surface area (milligrams per meter-squared).

2. The risk of secondary leukemia following childhood cancer therapy was found to be due almost entirely to alkylating agent therapy for the initial primary cancer. No increased risk was found for radiation

therapy. Alkylating agent therapy was associated with a significantly increased risk, reaching 20-fold in the highest dose categories after adjusting for radiation dose.

3. The risk of secondary bone cancer following childhood cancer therapy was found to be largely due to radiotherapy for the initial primary cancer, although an elevated risk from exposure to alkylating agents was also suggested.

4. An interview study of 1,362 breast cancer cases and 1,250 controls identified through a multi-center screening program allowed evaluation of effects of thyroid disease and supplementation on breast cancer risk. A previous diagnosis of treated thyroid disease was not associated with an excess risk, nor were any specific diagnoses, including hypothyroidism, hyperthyroidism, or goiter.

5. Data from the case-control study of breast cancer patients who developed endometrial cancer indicated a significant risk associated with estrogen therapy. All known risk factors for endometrial cancer were also observed in this study of multiple primary malignancies.

6. Although men with testis cancer were found to be at a two-fold risk of developing a second malignancy, chemotherapy and radiotherapy appeared to be associated with only a small proportion of the excess cancers, suggesting that most of the risk may be due to factors other than therapy. This study, however, included men treated for testis cancer in large part before 1970, prior to when chemotherapy became a more prevalent form of therapy.

7. An evaluation of the risk of leukemia following chemotherapy for ovarian cancer indicated that melphalan was significantly more hazardous than cyclophosphamide.

8. The survey of multiple primary cancers in Connecticut and Denmark found that 253,536 cancer patients reported to the Connecticut Tumor Registry during 1935-82 had a 31% increased risk of developing a second primary cancer, whereas, among 379,941 patients in Denmark (1943-80), a deficit of second primary cancers occurred (RR=0.9). In Connecticut, persons who survived more than 30 years after the diagnosis of their first cancer were at even higher risk, 49%. Over one million person-years of observation were recorded, and the excess risk of developing a new cancer was 346/100,000/year. Tissue susceptibility and common carcinogenic exposures were likely explanations for the frequent occurrence of many second cancers, particularly those known to be related to cigarette smoking and/or alcohol consumption. Persons with epithelial cancers of the lung, larynx, esophagus, buccal cavity and pharynx, for example, were particularly prone to developing new epithelial cancers in the same or contiguous tissue. A notable finding was the very high risk of cancers of the lung, larynx, buccal cavity and pharynx observed among cervical cancer patients, suggesting the possiblity of a common etiology with

cigarette smoking. The intriguing association between cancers of the colon, uterine corpus, breast and ovary was confirmed in the Connecticut data, indicating the possible influence of hormonal or dietary factors. Patients with prostate cancer had a significantly low risk for second cancer development, which may reflect an underascertainment of second primaries in patients of advanced age. Radiotherapy may have caused second cancers of the rectum and other sites among patients with female genital tract cancers, and leukemia was seen in excess after radiotherapy for uterine corpus cancer. In addition, chemotherapy was associated with an increase risk of acute non-lymphocytic leukemia among patients with multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary. Large numbers of patients with cancers of the rarer sites, i.e., of the eye, were available for study; and for most of these sites, a high risk of second tumors was found which persisted over time. Numerous new associations were identified for future study.

In Denmark, the findings with regard to overall risks for developing new cancers were not clear cut. This may have been due to reporting practices, for which second leukemias following hematopoietic malignancies were infrequently reported, and coding practices, for which cancers of paired organs, such as the breast, were counted only once as were multiple tumors in the same organ, such as colon.

9. The population-based case-control study of thyroid cancer did not find positive associations with the use of exogenous estrogens, oral contraceptives, alcohol, or most commonly used drugs. New associations, however, were suggested for the use of diuretics (RR=1.7), prior history of benign thyroid nodules (RR=52), goiter (RR=6.6) and benign breast disease (RR=2.0), and for a family history of thyroid cancer (RR=3.5).

10. Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a nine-fold increased risk of acute non-lymphocytic leukemia was found. The increased risk first appeared 2 years after the breast cancer diagnosis, was highest in 5-year survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1).

Significance to Biomedical Research and the Program of the Institute:

Studies of cancer patients treated with alkylating agents have observed high risks of leukemia and underscore the need for caution when such treatments are considered for patients at low risk of relapse, or for patients with various non-malignant diseases. As oncologists extend the techniques of adjuvant chemotherapy that have recently proven so successful in the management of breast cancer to patients with other cancers or with earlier stages of disease, drug toxicity becomes an increasingly important consideration. It is clear that any benefit derived from the adjuvant use of alkylating agents must

be carefully weighed against the small but demonstrable risk of therapy-associated leukemia. In addition, the possibility exists that some cytotoxic drugs may be less hazardous than others; and more detailed studies are needed of patients who have been exposed to specific cytotoxic agents, especially antimetabolites, and to different dose schedules or different regimens of therapy. In many instances, it is clear that late death from acute non-lymphocytic leukemia in some patients is certainly preferable to early death from a serious cancer in most patients, but the issue is more complex when these drugs are given in adjuvant fashion to patients in whom prolonged survival and prolonged therapy can be anticipated. In addition, the study of drug exposure has been one of the fruitful areas for identification of carcinogens in humans, and subsequent opportunities may exist for preventive programs and insights into the biological mechanisms in cancer etiology.

Proposed Course:

1. It is intended to continue the systematic monitoring of the long-term toxic effects (including carcinogenicity) of a number of therapeutic agents using the treatment of specific cancers (see also Project No. Z01CP04412-09 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-09 EEB, "Studies of Persons at High Risk of Cancer"). This will be done in collaboration with the Division of Cancer Treatment and the Environmental Epidemiology Branch as outlined in the Methods. Cohort studies currently being initiated include women with breast cancer treated with adjuvant chemotherapy in randomized clinical trials and in population-based cancer registry reporting areas. These efforts are being supplemented, where appropriate, by case-control studies of specifically suspect constellations of double-primary malignancies. These evaluations will involve medical record abstractions of therapy administered to patients who developed certain combinations of primary malignancies, compared with those with the same primary malignancy who did not develop a subsequent malignancy.

2. The analysis of ovarian cancer trials and the extended clinical trial patient series will be completed. A dose-response paper on the risk of leukemia and pre-leukemia following nitrosourea therapy for gastrointestinal cancer will be completed. From these, and previously reported studies, a decision will be made concerning a summary paper on the risk of leukemia following various dose levels of alkylating agents.

3. The analysis of case-control studies of second malignancies following treatment for childhood cancer will continue with respect to quantification of risk of individual second tumors following chemotherapeutic exposures.

4. The analysis of the risk of leukemia and second malignancies following chemotherapy exposures in several clinical trials conducted by the Veterans Administration Surgical Oncology Group will be completed.

5. The analysis of the large-scale case-control study of breast cancer patients who developed endometrial cancer in Connecticut, California, Iowa, Louisiana, and Denmark will be completed.

6. Analyses will be completed on the risk of second cancers following childhood malignancies, the risk of second cancers following adjuvant therapy for lung and colorectal cancer, and the risk of leukemia following treatment for ovarian cancer and for breast cancer. These studies should more clearly describe dose-effect relationships and clarify differential host responses to specific drugs.

7. If the study of epileptic patients and their offspring proves feasible, we will consider a case-control study of children who develop cancer in order to evaluate the possible transplacental carcinogenicity of anti-convulsive drugs.

8. Possible late effects following isoniazid therapy for pulmonary tuberculosis will be further evaluated in large-scale mortality studies in Connecticut and Massachusetts.

9. If the case-control study of chemotherapy-induced leukemia among breast cancer patients in Connecticut proves feasible, we will consider extending the study to additional SEER registries, and possibly Denmark.

10. The possible carcinogenic risk of phenothiazines will be evaluated in a large case-control study conducted among participants in the Breast Cancer Detection Demonstration Project.

11. The relationship between phenobarbital, spironolactone, and other drug exposures with thyroid disease will be evaluated in the HANES (Health and Nutrition Evaluation Survey) data base.

12. The risk of commonly used drugs will be evaluated in a case-control study of over 2,000 cases of leukemia and lymphoma and 2,000 matched controls using the resources of pre-paid health plans in California and Oregon.

Publications:

Boice, J. D., Jr. and Fraumeni, J. F., Jr.: Second cancer following cancer of the respiratory system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Boice, J. D., Jr., Storm, H. H., Curtis, R. E., Jensen, O. M., Kleinerman, R. A., Jensen, H. S., Flannery, J. T. and Fraumeni, J. F., Jr.: Introduction to the study of multiple primary cancers. Natl. Cancer Inst. Monogr. (In Press)

Boice, J. D., Jr., Storm, H. H., Curtis, R. E., Jensen, O. M., Kleinerman, R. A., Jensen, H. S., Flannery, J. T. and Fraumeni, J. F., Jr.: Multiple primary cancers in Connecticut and Denmark. Natl. Cancer Inst. Monogr. (In Press)

Boice, J. D., Jr., Storm, H. H., Curtis, R. E., Jensen, O. M., Kleinerman, R. A., Jensen, H. S., Fraumeni, J. F., Jr. and Flannery, J. T. (Eds.): Multiple Primary Cancers in Connecticut and Denmark. Natl. Cancer Inst. Monogr. (In Press)

Brinton, L. A., Hoffman, D. A., Hoover, R. and Fraumeni, J. F., Jr.: Relationship of thyroid disease and use of thyroid supplements to breast cancer risk. J. Chronic Dis. 37: 877-883, 1984.

Brinton, L. A., Hoffman, D. S., Hoover, R. and Fraumeni, J. F., Jr.: Variance and dissent: The authors' reply. J. Chronic Dis. 37: 891-893, 1984.

Curtis, R. E., Boice, J. D., Jr., Kleinerman, R. A. and Fraumeni, J. F. Jr.: Multiple primary cancer in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Curtis, R. E., Hoover, R., Kleinerman, R. A. and Harvey, E. B.: Second cancer following cancer of the female genital system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Curtis, R. E., Kennedy, B. J., Myers, M. H. and Hankey, B. F.: Evaluation of AJC stomach cancer staging using the SEER population. Semin. Oncol. 12: 21-31, 1985.

Ewertz, M., Machado, S. G., Boice, J. D., Jr. and Jensen, O. M.: Endometrial cancer following treatment for breast cancer: A case-control study in Denmark. Br. J. Cancer 50: 687-692, 1984.

Flannery, J. T., Boice, J. D., Jr., DeVesa, S. S., Kleinerman, R. A., Curtis, R. E. and Fraumeni, J. F., Jr.: Cancer registration in Connecticut and the study of multiple primary cancer, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Greene, M. H. and Wilson, J.: Second cancer following lymphatic and hematopoietic cancers in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Harvey, E. B. and Brinton, L. A.: Second cancer following cancer of the breast in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Hoar, S. K., Wilson, J., Blot, W. J., McLaughlin, J. K., Winn, D. and Kantor, A. F.: Second cancer following cancer of the digestive system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Kantor, A. F. and McLaughlin, J. K.: Second cancer following cancer of the urinary system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Kleinerman, R. A., Liebermann, J. V. and Li, F. P.: Second cancer following cancer of the male genital system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Tucker, M. A., Boice, J. D., Jr. and Hoffman, D. A.: Second cancer following cutaneous melanoma, and cancers of the brain, thyroid, connective tissue, bone and eye in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

Winn, D. M. and Blot, W. J.: Second cancer following cancer of the buccal cavity and pharynx in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. (In Press)

ANNUAL REPORT OF

THE EXTRAMURAL PROGRAMS BRANCH

NATIONAL CANCER INSTITUTE

October 1, 1984 through September 30, 1985

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), formerly the Special Programs Branch, is a component of the Epidemiology and Biostatistics Program and is responsible for those grants, cooperative agreements, and extramural contracts focused on epidemiology and biostatistics. To the extent possible, the Branch strives to facilitate multidisciplinary approaches to research in these areas. This symbiotic potential extends beyond the internal activities of EPB to the extramural community where interest in multidisciplinary efforts is increasingly evident. No rigid boundaries exist between the individual programs comprising the EPB. Indeed, as is evident from the program descriptions to follow, the activities of the Branch involve a high degree of integration and cooperative interaction between the respective program directors.

During the past year it has become increasingly evident that a widespread perception exists in the community of extramural epidemiologists that, despite the public health importance of the field, it has failed to show an adequate rate of growth over the past several years. In an attempt to make more explicit the basis for this perception, our branch held an informal meeting with a small group of individuals who are active competitors for epidemiologic research grants. The group included members of our divisional Board of Scientific Counselors, grantees in the epidemiologic area (both R01 and P01) as well as investigators responsible for major academic programs in the area. Available as resources for the discussion were members of the extramural staff concerned with epidemiologic activities as well as individuals involved in the grants review and administration process and NCI training grant activities. The meeting appeared productive for all parties. NCI staff gained a better understanding of the perceptions of extramural investigators in this area; the investigators themselves gained a better understanding of the overall process underlying research grant review, selection and award. It is hoped that some steps may be taken in the future to further develop some of the concepts and suggestions which emerged during the discussion.

It should be pointed out that, as a result of early preparation, some discrepancies will occur throughout this report when numbers of research grants or total support levels are discussed. In general, discussions of program areas are restricted to those research grants active in the period October 1, 1984 through June 1, 1985; additional research grants will be funded during the remaining four months of the fiscal year but their individual focus and exact support level is uncertain at this time. Based on past experience, we are able to estimate their impact on budget at the Branch level, but not their impact on individual programs within the Branch.

Biometry: Although primarily composed of research grant activities, contracts and interagency agreements are also being utilized to determine the feasibility of linking existing data sources to provide epidemiologic resources to the extramural scientific community. This program area includes a wide variety of research activities, including mathematical models relevant to cancer biology; statistical techniques useful in evaluating the effects of potential carcinogens; determining the effects of patient characteristics on survival analysis or the analysis of competing risks; record linkage for investigations involving special population groups and cancer registries or death lists; the relation of cancer susceptibility to cytogenetics and somatic cell genetics; design of statistical techniques to evaluate carcinogen screening tests and procedures; and improved methodologies for evaluating estimates of cancer risk from low-dose exposure to carcinogens.

Epidemiology: This program area is primarily supported by the research grants mechanism. Contracts have been used only for the support of initiatives related to the Acquired Immunodeficiency Syndrome (AIDS) which require the identification and follow-up of individuals in specific high-risk groups. Research areas of interest include: investigations focusing on the natural history of neoplasia in humans; the incidence and prevalence of various human cancers as a function of geographic location; etiologic risk factors (both intrinsic and extrinsic) related to human cancer; opportunities for preventive action; and improved methodologies for the design and conduct of epidemiologic studies.

The program also contains emphasis areas in occupational carcinogenesis; the epidemiology of AIDS and AIDS-related neoplasms; nutritional epidemiology; and the epidemiology of tobacco-related cancers. Although our current involvement with both Nutrition and Smoking and Health has been diminished by the transfer of those basic science grants focusing on nutrition and tobacco toxicology to another branch, we are attempting to strengthen these areas by soliciting the submission of investigator-initiated epidemiologic applications. Requests for Applications (RFAs) on "Involuntary Exposure to Tobacco Smoke and Cancer Risk," "Dietary Markers for Epidemiologic Studies of Cancer" and "Obesity and Cancer Risk in Women" have been issued during the past year. Responses have now been received and evaluated and we expect awards to be made during this fiscal year.

AIDS Epidemiology: An AIDS Epidemiology Program was initiated in response to the developing epidemic of Acquired Immunodeficiency Syndrome, with its associated opportunistic infections and malignancies (primarily Kaposi's sarcoma). The emphasis of this program is to support research focusing on the natural history of AIDS as well as on the elucidation of risk factors and etiologic mechanisms for AIDS. In addition, the program is supporting epidemiologic studies of cancers of the anogenital area to determine whether there are risk factors and etiologies in common with AIDS. This activity is supported primarily through grants and cooperative agreements. In addition, the Branch is collaborating with the National Institute

of Allergy and Infectious Diseases (NIAID) to support contracts for the study of the natural history of AIDS in homosexual men.

During this fiscal year, we supported ten assistance awards and contributed $1.0 million in the support of three contracts with NIAID. Three of the assistance awards were cooperative agreements resulting from an RFA and the other seven were funded as traditional research grants.

Biochemical Epidemiology: Specific program emphasis in the area of Biochemical Epidemiology continues to be stressed. Our efforts to stimulate research in this area were marked by the issuance of a request for applications and a $1.8 million budget reserve from Division funds for each year of the period 1983-1986. The response was enthusiastic and the RFA was reissued in fiscal year 1984 with an additional budget allocation of $1.2 million in each year of the period 1985-1987. Few responses were concerned specifically with the development or validation of laboratory procedures which show promise of epidemiologic usefulness. We are attempting to deal with this problem by the issuance of an additional RFA entitled "Development, Validation and Application of Biochemical Markers of Human Exposure for Use in Epidemiologic Studies."

Small Business Innovation Research Program (SBIR): This program was established by Congress in 1982 for the purpose of stimulating small business participation in Federal research and development (R&D) projects. The Act requires each Federal agency having an extramural research and development budget in excess of $100,000,000 to set aside a proportion of that budget (0.2% in fiscal year 1983 and rising gradually to 1.25% in fiscal years 1986 through 1988) for awards to be made under this program. The program provides for Phase I (feasibility studies of 6 month duration and costing no more than $50,000) and Phase II (substantive research efforts of no more than 2 year duration in an amount not exceeding a total of $500,000) awards.

The program was initiated at NIH by announcing the availability of funding for investigator-initiated research grants from organizations meeting the stated eligibility criteria. In fiscal years 1983 and 1984 the National Cancer Institute had considerable difficulty in expending the required proportion of its R&D budget for the support of high quality grant applications under this program. Those applications funded were largely in basic science areas and the Epidemiology and Biostatistics Program derived little benefit from the sizeable amount expended in NCI for this Program. As a result, it was decided to issue a request for contract proposals in fiscal year 1985. Our Program area determined that it would be to our benefit to participate in this solicitation.

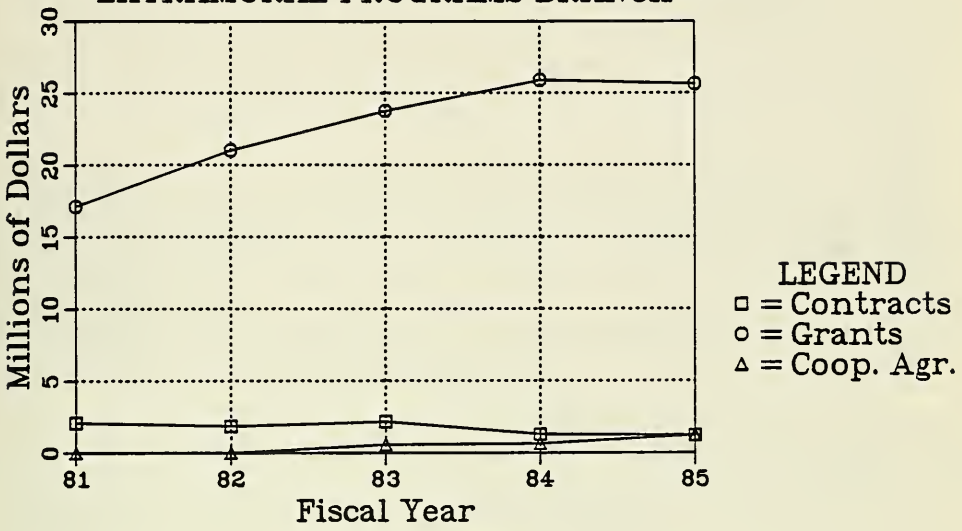
The Extramural Programs Branch, in close collaboration with key intramural investigators, developed a set of work statements for activities deemed suitable for small business efforts. The topics were chosen from among those which Epidemiology and Biostatistics Program staff felt were clearly needed but which would otherwise not be implemented because of fiscal constraints. Six such topics were advertised. Thirty seven proposals were received and are currently under review. Awards are anticipated for the successful proposals during this fiscal year.

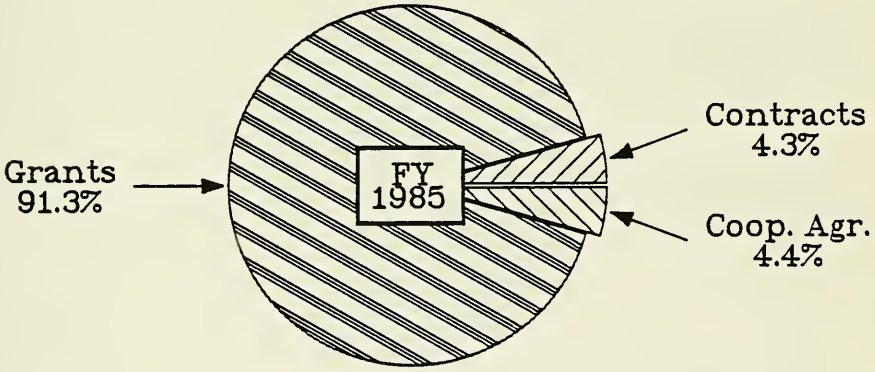
The following figures attempt to provide some perspective on the balance of activities within the Branch as well as an overview of developments over recent fiscal years. As shown in Figure 1, we have begun to use the cooperative agreement mechanism to support selected activities. Its use to date has been restricted

to the support of AIDS-related initiatives in which it is important that NCI staff be closely involved to assist in the exchange of information and biologic materials. It should also be noted that the extent of utilization of the contract mechanism for research support continues to fall.

Figure 2 illustrates the continued growth of Branch programs. The categories of AIDS-related epidemiology and biochemical epidemiology assumed a separate identity in 1983. The first because of the emergence of a serious epidemic and the latter because of special research opportunities in this area. The identification of biochemical epidemiology as a separate category of activities initially diminished the size of the general epidemiology category, since relevant activities would otherwise have been assigned there. The fall in smoking and nutrition-related activities in 1984 is largely a consequence of the transfer of basic studies in these areas to another branch. Several RFAs have been prepared which are serving to increase our level of epidemiologic involvement in these areas.

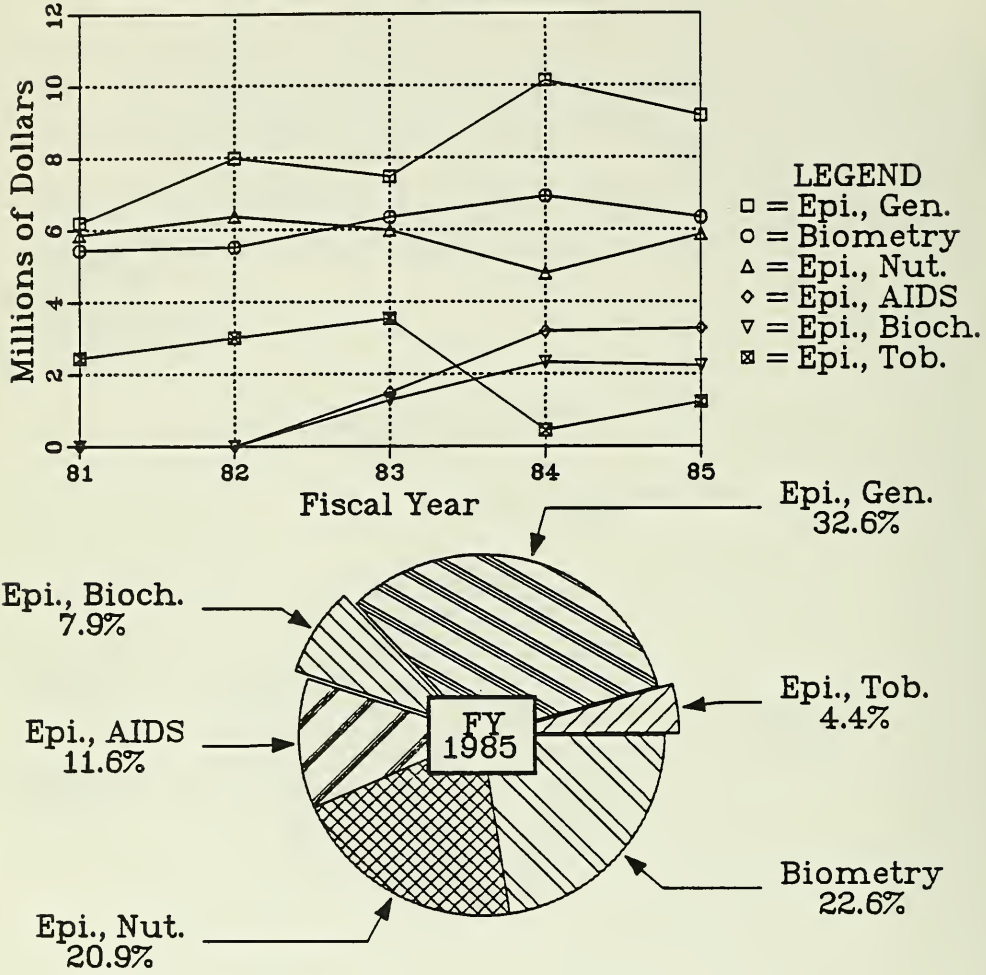
FIGURE I
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH





FISCAL YEAR 1985 ESTIMATE	$(Millions)	Percent
Contracts	1.22	4.3
Grants	25.65	91.3
Cooperative	1.23	4.4
TOTAL	28.10	100.0

FIGURE II
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH



FISCAL YEAR 1985 ESTIMATE	$(Millions)	Percent
Biometry	6.34	22.6
Epidemiology, general	9.16	32.6
Epidemiology, biochemical	2.23	7.9
Epidemiology, AIDS related	3.27	11.6
Epidemiology, nutrition related	5.87	20.9
Epidemiology, tobacco related	1.23	4.4
TOTAL	28.10	100.0

BIOMETRY PROGRAM

Description: The Biometry program consists of developmental studies in biostatistics and genetics related to cancer epidemiology. The program currently supports 44 Traditional Investigator Originated grants (R01), four New Investigator Awards (R23), three Program Project grants (P01), two Interagency Agreements and one Research Resource Contract. Most of the investigators are well established in their fields and are from leading universities and cancer centers.

Since its inception in 1979, the number of grants in the program has grown by a factor of three. However, the dollars have remained fairly constant. This is attributable to growth in the areas of theoretical biostatistics and computer science. Over half (56%) of current grants are in these areas yet they account for only 38% of program dollars. Genetics has grown more slowly in terms of number of grants (26%) but more rapidly in terms of dollars (42%). Most genetic projects are no longer simple pedigree studies, but rather ones that now include costly biological components. Large computer center grants have increasingly given way to individual biostatisticians coming into the program with small grants which permit them to focus on problems of particular interest.

Research Accomplishments: The Biometry program continues to support theoretical biostatisticians working in the area of clinical trials. These investigators have shown great interest in all aspects of this area from experimental design to final data analyses. Problems currently under investigation are sampling and recruitment strategies, stopping rules, treatment allocation schemes, quality control and compliance evaluation, statistical methodologies allowing for sequential entrance, progressive censoring, missing data, and loss to follow-up (7, 28, 51, 68, 85, 90, 95, 136, 157). This year attention has been given to interpretation of trial results in relation to other published trials. This work was prompted by the observation that studies in which the observed efficacy of the treatment is high are more likely to be reported than if the efficacy is average or poor (7).

Mathematical modeling of biological phenomena has accelerated as experimental methods and computer capabilites have facilitated the collection of large quantities of data on systems fundamental to life. Biostatisticians and allied scientists are now reexamining these data in light of recent advances in their respective fields of expertise (5, 12, 72, 88, 132). Since models are initially based on biological intuition and/or rather sparse observations, they are being tested and retested against different data sets under differing conditions. If sufficiently refined, such models should contribute to an overall understanding of underlying mechanisms of carcinogenesis. Cell kinetics is currently the most fruitful area for modeling because the data are essentially free of the inadequacies often present in epidemiologic studies, and the analytic methods and techniques are available. One aim of such modeling is to develop procedures for obtaining estimates of cell cycle traverse characteristics in malignant and normal cells before and after exposures/treatments and to use these estimates to promote knowledge of cell biology, cancer etiology, diagnosis and prognosis (84, 89, 92, 158).

Epidemiologic modeling suffers from a vagueness due to insufficient data collected non-uniformly over time. It is generally believed that most human cancers develop as the result of a succession of steps occurring over a period of many years. Two mathematical models of the process, one involving two stages and one involving multiple stages, have been proposed to account for observations from a number of

studies of various cancer sites. Both permit analytic evaluation of temporal variables, e.g., age at first exposure, duration of exposure, age at risk, and time from first exposure to detectable disease. These models are simplifications of complex processes, but they do have heuristic value in that they focus on possible temporal mechanisms, e.g., whether the carcinogenic exposure exerts its influence early or late in the process. The hypotheses generated by fitting these models to appropriate epidemiologic observations should, if sufficiently refined, shed light on mechanisms underlying the carcinogenic process in terms of the initiation and promotion phases along with differences in reversibility, i.e., does cessation of carcinogen exposure result in a reduced risk or does the induced risk continue (88, 89, 147)? Several investigators in the program have had the opportunity to explore mathematical models of the carcinogenic effects of single dose radiation exposure utilizing the atomic bomb survivor data, perhaps one of the most complete data sets currently available for modeling purposes, courtesy of the Radiation Effects Research Foundation, Hiroshima, Japan (50, 68, 104, 137).

The traditional approach of clinical geneticists has been to collect information on individuals who have been brought to their attention because of unusual clusters of disease. These efforts have resulted in providing descriptions of traits due to simple dominant or recessive genes, but have failed to yield insights into complex situations involving age and/or sex specificity, genetic heterogeneity, multiple loci, or gene-environment interactions. Recognition of family clustering, however, has been valuable in that it has led to the establishment of population based genealogies with fully ascertained families which can now be used in a more productive manner (77, 103, 118, 124, 127, 141).

During the past few years rapid strides have been made in DNA technology such that the presence or absence of a restriction site is a polymorphic marker for detection of a specific disease. The use of such markers will accelerate gene mapping of single locus traits. Mapping of the human genome has long been the goal of genetic researchers but progress was limited by the inadequate number of polymorphic protein and antigenic markers. Now, however, with the advent of DNA polymorphisms, a library of random single copy DNA probes is being created which, when complete, should permit detection of DNA sequence polymorphisms in an individual's DNA (8, 118). Each probe would define a specific locus in the genome. In conjunction with family studies in appropriate pedigrees these could be arranged in specific chromosomal groups and thereby produce a genetic map. Investigators in this area are extremely enthusiastic about the future of this work, its potential contribution to knowledge of cancer etiology and prospects for the identification of high risk individuals. Other geneticists are utilizing advances in image processing to standardize techniques for the separation of proteins by automating 2D-gel electrophoresis in order to study germinal and somatic cell mutations in relation to cancer etiology (50, 158).

Childhood cancers, although relatively rare, are being studied because of their unique characteristics. These include their short latency period and the ready availability of parents for obtaining environmental exposure and family history data. While some environmental agents are clearly associated with adult human cancers, few have been associated with childhood cancers, presumably because of lengthy latency periods usually involved in environmental carcinogenesis. Childhood cancers would thus appear to be either genetic or sporadic in origin. A few have actually been found to have familial components, e.g., Wilms' tumor, retinoblastoma, and soft-tissue sarcomas. Assessments are being made of risk of second tumors in children surviving three years following a first cancer, including tumors

which may be attributable to treatment modalities. Further, the risk of first tumor is being assessed in relation to parents' prior exposure to known or potential carcinogenic agents (83, 84, 93, 124, 125, 126).

One investigator has assembled an international registry of families who have been affected by Bloom's syndrome over the last 30 years. Cases have been ascertained through reports in the literature or direct referral. There are presently 109 confirmed entries. The registry has become a vehicle for the surveillance of the Bloom's syndrome population with respect to incidence, age of onset, and distribution of types of neoplasia and as a central repository for pedigree information on family members. The latter provides a source of specimens such as blood cells, tissue culture cell lines and tumor DNA for distribution to other laboratories. The most interesting clinical feature of the syndrome is cancer proneness. It is unlike most genetic disorders which predispose to cancer in that it does not appear to predispose to one type of cancer but rather to several.

The Interagency Agreements involve efforts to develop a national data resource for the investigation of cancer in the workplace. The United States currently has no such resource, although the essential elements have been collected and do exist in the data bases of various Federal agencies. The Agreements are assessing the feasibility of linking these data bases to obtain essential elements (159, 164). The contract is supporting a registry of persons with primary immune deficiency states who subsequently develop cancer (161). The registry is available to the extramural research community to enhance investigations in this interesting area.

Projections: The growth of the Biometry program is dependent upon the special mathematical, statistical and computer skills of investigators and on their ability to extend their expertise into the biomedical scientific community. While many investigators are submitting proposals, those who address specific biomedical or epidemiologic problems are more likely to be funded than are the pure theorists. These decisions are made through peer review. The problems associated with the lack of a standing Initial Review Group remains frustrating to investigators and staff. Staff will however, continue to work with the Division of Research Grants to promote appropriate grant review.

Program staff continues to work with current and prospective applicants to encourage them to establish collaboration with other scientists and oncologists to lend biological credence to their theoretical concepts and to obtain data for testing new methodologies. Publications will continue to appear in theoretical and applied refereed journals.

EPIDEMIOLOGY PROGRAM

Description: The cancer epidemiology extramural research program supports descriptive, analytic, and methodologic studies. Inquiries into the natural history of neoplasia in humans, elucidation of the role of precursor lesions, studies of the incidence, prevalence and mortality from human cancers, and examination of geographic distributions or time trends are appropriately assigned to the program.

The program is particularly interested in analytic epidemiologic studies of host factors and environmental, occupational or lifestyle exposures including a number of specific agents known or suspect to influence cancer risk. There is strong interest in supporting research which elucidates causal associations and mechanisms of carcinogenesis in human populations, and in basic epidemiologic research which provides information essential to preventive intervention.

In order to improve the specificity and accuracy of research findings, the program supports methodologic studies which relate to the design, conduct and analysis of epidemiologic investigations, and which improve the capacity to distinguish contributions of multiple risk factors. This support includes the development and characterization of laboratory procedures.

Research Accomplishments: Among the most exciting findings are those relating to risks of cancer associated with viral infections. Epstein-Barr virus (EBV) has been reported to be associated with Hodgkin's disease (HD) (33, 47). Hodgkin's disease cases usually have elevated EBV capsid antibody titers, and the occurrence of HD among persons with a history of EBV infectious mononucleosis is two to three times higher than expected. The prevalence and levels of antibodies against EBV and related viruses were ascertained in 304 cases of HD and 285 of their siblings in a population-based study. The most significant finding was that antibody titers to the viral capsid antigen of EBV were elevated in 39% of the cases and in only 14% of the sibling-controls; the relative risk adjusted for age and sex was 4.1. The geometric mean titer was three times higher among cases (175.6 vs. 58.1). Subjects who reported a history of infectious mononucleosis had higher titers than those who did not. Cases also had elevated titers against the early antigen of EBV, the D Component being most prominent. A significantly higher proportion of cases had titers of 1:40 or more against cytomegalovirus (CMV). However, the overall prevalence of CMV antibody titers was relatively low and not consistently higher among cases. These findings support the hypothesis that EBV may play a role in the pathogenesis of HD; the findings neither confirm nor deny a possible role of CMV.

A prospective study (6) in Taiwan of the relationship between hepatitis B and primary hepatocellular carcinoma (PHC) revealed a relative risk of 190 associated with chronic infection; the primary source of infection for young children who are likely to become chronically infected is their mothers. Dr. Beasley, the Principal Investigator, was awarded the Faisal prize in recognition of the importance of his research on liver cancer. In collaboration with Blumberg (9), Beasley examined the relationship of serum ferritin and transferrin levels to risk of cancer in a population of 21,513 male government workers who have been followed prospectively since 1975. The mean serum ferritin level was higher at the start of the study in 192 men who had died of cancer or developed PHC as of July 1983, compared to their controls; the mean serum transferrin was lower in men who died of cancers other than PHC. These results are consistent with the hypothesis that increased iron stores increase risk of cancer. The estimate of relative risk of cancer is 2.9 for a man with ferritin of 200 ng/ml and transferrin of 200 mg/dl compared to a man with levels of 20 and 400 respectively. These serum iron-binding protein levels are at the extremes of the "normal" range. Men who subsequently died of cancer had lower hemoglobin, lower hematocrit, lower albumin, and higher globulin at the start of the study than the controls. These differences could result from chronically higher iron stores which might increase the frequency or severity of infections over the span of life. This same increased iron level might also increase the risk of cancer.

To determine whether or not asymptomatic hepatitis B virus infection is a risk factor for hepatocellular carcinoma in the United States, index and control groups were identified within the American Red Cross Donor Deferral Register, a computerized record of blood donors who had been rejected or placed under surveillance for reasons relating to viral hepatitis. A total of 15,166 individuals, representing

55,805 person-years of follow-up, composed the index group of individuals who were reactive for hepatitis B surface antigen. The control group consisted of 18,144 donors, representing 59,092 person-years of follow-up, who were HBsAg-nonreactive donors implicated in multiple-unit post-transfusion hepatitis cases. Identifying information for each individual in the study was submitted to the Social Security Administration (SSA) where it was searched against the central files; a total of 328 deaths were identified among the 76.1% matches, and death records were obtained for 70.1% of the individuals SSA reported as dead. A total of 31 (23%) of all deaths in the index group were in some way liver-related, whereas there was only one such death in the control group. Six cases of hepatoma and seven of cirrhosis (all males) were identified in the index group. Relative risks of 4.48, 15.67 and 13.43 were calculated for deaths due to alcohol abuse, cirrhosis and hepatoma, respectively, using a dummy value of 0.5 deaths in the control group. A standardized mortality ratio (SMR) of 26.78 was calculated for hepatoma in the index group with reference to the 1975 U.S. Vital Statistics. The predominance of blacks among the hepatoma cases (4/6) was striking, particularly since they represent only about 4% of the normal donor population. Three of the hepatoma deaths in blacks occurred during their third decade, yielding an SMR of 130 for the age/race group.

The incidence of primary liver cancer is increasing as shown in an analysis of 30 populations reported in "Cancer Incidence in Five Continents" (9). After adjustment for time trends, log incidence increased linearly with log age. Liver cancer risk increased more rapidly with age than that of colon cancer, stomach cancer or lung cancer in smokers. Over the past 20 years, most populations have been found to have increasing age-adjusted liver cancer incidence. There was no correlation between changes in rates and magnitude of rates. Male rates are higher than female rates and the ratio of the two tends to be higher in high-risk areas.

Fifty-seven female residents of King and Pierce Counties (Washington State) with a new diagnosis of in situ or invasive vulvar carcinoma during 1976-1979 were interviewed concerning their menstrual, reproductive and medical histories (27). A random sample of women residing in the same area was interviewed for comparison. A greater proportion of women with in situ vulvar tumors than control subjects were of low educational level, reported a history of contraceptive use, experienced early age at first birth, late age at menopause, or were current or former cigarette smokers. Menstrual and reproductive factors were similar between women with invasive vulvar cancer and controls, but a greater proportion of cases reported a history of diabetes and of cigarette smoking. The factors found in this study to be associated with in situ vulvar carcinoma are similar to those observed among women with cervical cancer. It is suggested that in situ vulvar and cervical tumors may share some common etiologies since the vulva and cervix both are derived from cloacal tissue, and neoplasms of the two sites occur together more often than would be expected by chance.

There are some interesting preliminary findings from a case-control study of anal cancer (26). Cases consist of all men and women, aged 30-69, diagnosed as having anal cancer from 1978 to 1986 identified by the Washington State and the British Columbia tumor registries. Controls consist of colon cancer patients from the practice of the physician who treated the case, matched for year of diagnosis, race, sex, and age (5 year groups). Analysis of the first 98 cases and controls suggests that for men, homosexuality, anal intercourse and smoking were all important risk factors for anal cancer. For women, genital warts, anal intercourse and smoking were important.

In a follow-up of a cohort of 143,594 people whose pharmacy records had been computer stored from July 1969 to August 1973 (38), no negative relationship was found between digitalis and subsequent cancer, contrary to a decreased risk of breast cancer among women taking digitalis reported by Goldin and Safa. Instead, digitalis was positively associated with risk of cancer of the colon, lung and prostate. Follow-up data until 1980 show that use of digitalis continued to be associated with cancers of the lung and colon but its association with prostate cancer was no longer significant. Breast cancer incidence showed no inverse relation to digitalis use. When 1980 cancer mortality was the endpoint rather than cancer incidence, one death from breast cancer was observed vs. 3.72 expected ($p=0.11$). Thus, digitalis does not appear to prevent breast cancer from occurring or being diagnosed, but the question of digitalis slowing the growth of breast cancer, once it is present, remains open. The initial observation of a "protective" effect of digitalis may have been due to an inappropriate control group since a high proportion of persons dying from causes other than cancer, among which cardiac diseases are well represented, are likely to have used digitalis.

Questions of cancer risk associated with exogenous hormones, and indirectly associated with medications which modify endogenous hormones, continue to interest investigators. For example, it has been postulated that reserpine might increase women's breast cancer risk indirectly through increasing their prolactin levels (53). Prolactin levels were measured in 15 women who had used reserpine for at least 5 years, in 15 women who had been taking other antihypertensives and in 15 women taking no antihypertensive medicines. Although reserpine users had significantly elevated prolactin levels, their mean level was only about 50% greater than the mean level of the combined results from the two control groups. Based on a statistical model of breast cancer incidence, it was calculated that such increases in prolactin in the post-menopausal period would be likely to cause only small increases in breast cancer risk, as has been observed in epidemiological studies.

Because of studies which associate menopausal estrogen supplementation with both increased risk of endometrial cancer and decreased risk of hip fractures, research relating to the use of estrogen supplements has a broad focus. By August 1984, a cohort study of 11,888 women residing in a Los Angeles retirement community had accumulated 23,579 woman-years of follow-up. The mortality rate for all causes of death was significantly reduced in current users ($p<0.001$) compared to never users. The mortality rate from acute myocardial infarction (MI) was also significantly reduced in current users ($p=0.056$). The reduction in the mortality rate for all causes and for acute MI among current users remained unchanged after adjusting for smoking and prior hysterectomy.

Since the early reports of increased risk of clear-cell adenocarcinoma in young women whose mothers received diethylstilbestrol (DES) during their gestation, there has been concern that male children might also be adversely affected. A study has been carried out to determine whether a cohort of males exposed in utero to DES had a higher frequency of urogenital abnormalities than an unexposed cohort. Biases in selection of exposed and control participants were minimized by using medical records to select exposed and nonexposed study subjects. Of 828 exposed and 676 control men, a subgroup of 265 exposed men and 274 controls also underwent a special clinical examination. The investigators state that, overall, the data do not support the hypothesis that DES exposure of males in utero increased their risk of genitourinary abnormalities, infertility or testicular cancer. They believe that previously reported increased frequencies of these abnormalities in

DES-exposed men may have resulted from selection biases or differences in DES use, or both.

This finding is in contrast to conclusions reported from a descriptive study of germ-cell tumors in men and women over the past decade (52). This study examined data from Los Angeles and from the SEER registries to determine if the increasing incidence trend observed and reported for germ-cell tumors in males is paralleled by a similar increase in women. Data for the years 1972/1976 were compared with 1977/1981 in Los Angeles, and SEER data for the years 1973/1976 were compared with 1977/1980. In Los Angeles, sizeable increases in the incidence of malignant germ-cell tumors, both germinomas (including seminoma of the testis and dysgerminoma of the ovary) and teratomas (embryonal and extraembryonal cell types), occurred in the 15-34 age range between the two calendar periods. These trends were statistically significant in the 25-34 age group for both sexes. The largest increases occurred in the germinoma group for females and in the teratoma group for males. The SEER data also show substantial increases in incidence rates for the same age categories (15-24 and 25-34 years of age), although the magnitude of the increase is not as large as in Los Angeles. There is the possibility that the two histologic types of testicular and ovarian cancers may share some etiologic factors, including the possibility of in utero exposure to endogenous or exogenous hormones.

Several methodological studies completed during the year will contribute to future research. During 1984, one investigator (107) completed and reported on a validation study which indicated that interview data alone may be used for case-control comparisons of dental x-ray exposure, with some underestimation of risk. A study of the effects of storage on hormone levels (estrone, estradiol, estriol, testosterone, androstenedione, progesterone) revealed that day to day variations due to laboratory technique were more important than other factors in explaining differences in observed values. Alpha-fetoprotein levels did not show the laboratory variations but rather the levels decreased in proportion to the time the specimen had been stored, at a rate of 12% per year (22).

Projections: There is strong interest in fostering research collaboration and interaction between scientists working in basic carcinogenesis and those with special skills for conducting research involving humans. The development of several laboratory procedures which have a potential for detecting and quantifying actual exposure of individuals to viral agents or chemical carcinogens is exciting and provides a tremendous challenge at all levels.

Several problems impede advancement to some extent. One is the fact that administrative and geographic distances between these groups of investigators must be overcome. Another relates to a perceived financial instability which is burdening epidemiologic investigators and which sometimes discourages young epidemiologists before they have obtained their first job. Still another results from the fact that research at this interface between epidemiology and basic carcinogenesis is so new that there are no rules of conduct for structuring the research proposals or for determining when a procedure is ready for application in large-scale studies.

The area of epidemiologic research which seems most promising in the near term is that which relates to the role of viral agents, including the HTLV series, EBV, hepatitis B and human papilloma virus. Already, interesting findings are being reported and research will become much more informative as procedures which specifically identify the agent and the human host's reaction to infection become available for large-scale studies.

The value of earlier investment in a series of resources should become increasingly apparent as they are used by investigators over the next several years. The resources include statistical methods, population-based tumor registries and large pedigrees with documented disease experience. Taken together, these permit more refined studies which take account of several risk factors simultaneously and permit smaller diagnostic aggregations. These advances are prerequisite to laboratory estimation of risk factors.

AIDS-RELATED EPIDEMIOLOGY

Description: An AIDS Epidemiology Program at NCI began in the Branch in 1981 as a consequence of the burgeoning epidemic of Acquired Immunodeficiency Disease Syndrome (AIDS), with its associated opportunistic infections and malignancies (primarily Kaposi's sarcoma). The principal emphasis of this program is upon the delineation of risk factors and etiologic mechanisms for AIDS and AIDS-associated malignancies. In addition, the program is supporting epidemiologic studies of cancers of the anogenital area to determine whether there are risk factors and etiologies in common with AIDS. This activity is supported primarily through grants and cooperative agreements. This Branch also is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID) to support contracts for the study of the natural history of AIDS in homosexual men.

The finding by Gallo, et al., that the human T-cell lymphotropic virus-type III (HTLV-III) is the putative AIDS agent has markedly influenced all research in this area. Since the initial published reports of these findings in the spring of 1983, the vast body of data supports the etiologic role of HTLV-III as the AIDS virus. Epidemiologic studies continue to be important for the elucidation of relevant host and co-factors for the expression of disease, asymptomatic carrier state, or abortive infection. The AIDS epidemic continues unabated with a total of 18,000 cases predicted by the end of 1986. A growing area of concern is the increasing risk of transmission into heterosexual populations through sexual contacts with prostitutes, intravenous drug abusers, or recipients of contaminated blood or blood products prior to development of clinical signs in the infected individuals.

Research Accomplishments: Several studies supported by the Branch are aimed at more clearly identifying the factors that place homosexual and bisexual men at high risk for the development of AIDS. A case-control study of Kaposi's sarcoma (KS) and AIDS in New York City is in its initial stages (113). It aims to describe the epidemiology of AIDS in terms of major risk factors and co-factors and to determine which of the involved factors best differentiate between the cases and the high risk individuals currently without AIDS (patients with lymphadenopathy of unknown cause, sexual partners and friends of AIDS cases, and male homosexual controls without AIDS prodromes). As in other studies, they have found that the ratio of T-helper to suppressor cells was significantly lower for the cases than for the asymptomatic controls (0.55 vs. 1.42, respectively). Prognosis for 2 year survival of the KS cases was related to this ratio, with 20% of cases surviving if that ratio was less than 1.0 upon entry as compared to 45% and 80% associated with ratios of 1.0-1.7 and greater than 1.7, respectively. Of 143 cases of KS-AIDS tested for HTLV-III antibody, 76% were positive by the ELISA test and 92% by the Western blot test. Prognosis was best for those KS cases negative for antibody by both tests.

Another case-control study of risk factors for KS-AIDS in New York City (80) has recruited a total of 16 cases and 50 controls as of the end of January 1985. Fifteen of the 16 cases were male homosexuals. However, the sixteenth case was a

lesbian intravenous drug abuser whose female partner, who has never used intravenous drugs, has symptoms of AIDS-related complex (ARC). Sera from both women are positive for HTLV-III antibodies. Histories indicate involvement in sexual activities that resulted in mutual exposures to blood due to abrasions and/or menstrual bleeding. This may be the first report of female to female spread of AIDS or ARC.

In a small prospective study in New York City (80), 40 initially asymptomatic homosexual men have been followed over a three year period. The prevalence of HTLV-III antibody increased from 20% in late 1981 to 36% in the summer of 1984, with receptive anal intercourse as the significant risk factor for seropositivity. The cumulative incidence of AIDS or suspected AIDS was 0% (0/23) for seronegative individuals and 71% (12/17) for those who were seropositive. In those men practicing receptive anal-genital intercourse, serum beta-2-microglobulin was elevated and, of 7 subjects with high levels at enrollment, 2 developed AIDS and 4 developed suspect AIDS. In a further study of the relationship to AIDS, this serum factor was found to be elevated in 96% of AIDS patients, 35% of asymptomatic homosexual men, and 1.5% of blood donors. Beta-2-microglobulin appears to be a sensitive, but not specific, manifestation of the disease process related to AIDS.

In a larger sample of 1100 cases of AIDS in New York City (80), the proportion of cases with KS was found to vary with risk group: 46% of male homosexuals, 27.8% of male homosexuals who also were intravenous drug abusers (IVDA), 12.5% of female IVDA, and only 3.8% of heterosexual male IVDA cases of AIDS. A subsequent study of 78 New York City IVDA (30 females and 48 males) found HTLV-III antibodies in 59%, with no differences by sex or cytomegalovirus (CMV) seropositivity. However, CMV-seropositivity was found in 87% of female versus 42% of male IVDA, and CMV-seropositive females had significantly more sexual partners in the past year than did seronegative female IVDA. These data (i.e., CMV-seropositivity rates lowest in male IVDA, intermediate in female IVDA, and highest in male homosexuals) suggest that there is a role for CMV (or an associated agent) transmitted in semen, as a cofactor for KS-AIDS.

This Branch is collaborating with NIAID to support a large five center contract effort to study the natural history of AIDS in homosexual men (160, 162, 163). Five thousand asymptomatic homosexual men (1,000 each from Baltimore, Chicago, Los Angeles, Pittsburgh, and San Francisco) have been recruited and will be followed semiannually for three years for the development of AIDS, AIDS-related symptoms, or malignancies. Subject recruitment only started in the spring of 1984. All centers now are entering the second semiannual revisit of the subjects. A bank of data (clinical, epidemiological, and tissue specimens) will be collected and available to investigators at the five institutions as well as to the general scientific community. In a large prospective study, etiologic hypotheses can be tested with more confidence than in smaller case-control studies. An example of the utility of this study is the testing of banked sera and lymphocytes for evidence of HTLV-III and the identification of risk factors for infection and later AIDS symptoms. Initial analyses of a random sample of about 100 sera from each center collected by November 1984 found that the prevalence of HTLV-III antibody seropositivity varied by region: 22% for Baltimore, 25% for Pittsburgh, 44% for Chicago, 54% for Los Angeles, and 55% for San Francisco. Antibody testing was performed by DuPont and by Electronucleonics (99.3% concordance), and DuPont has agreed to continue free ELISA testing of all further study specimens. Not unexpectedly, there was a significant association between seropositivity and number of lifetime partners, practice of receptive anorectal intercourse, lymphadenopathy and ARC, decreased T-helper cells, increased T-suppressor cells, and history of sexual

contact with AIDS-affected individuals. In addition, there was a clear age cohort effect, with the highest seropositive prevalence (45%) in age range 25-34 years and 6 to 20 years of regular homosexual activity. The public health significance of these findings is that 50% or more of the male homosexuals probably are free of the AIDS virus and should be encouraged to reduce their numbers of sexual partners to limit possible future infection.

Several studies are attempting to identify the biological mechanisms that may play critical etiologic roles in the manifestation of AIDS and AIDS-associated malignancies. In one project (30), serum IgG reactive with peripheral blood T-lymphocytes was present in only 5% of the healthy heterosexual males, in about one-third of the homosexual men without AIDS, and in almost two-thirds of the male AIDS cases. Sera from 22% (9/41) female prostitutes had similar antibodies. The immunosuppressive properties of sperm and semen have been documented in experimental animal systems. Spermatozoa have surface antigens cross-reactive with those on T-suppressor cells, and cell-free seminal fluids from healthy heterosexuals selectively activate suppressor cells. In the homosexual men, the route of sperm immunization and the exposure to heterologous spermatozoa may be a possible etiologic co-factor for AIDS.

Products have been found in the blood of AIDS patients which may contribute to the profound immunosuppression which characterizes this disease. Soluble suppressor factors (SSF) produced by peripheral blood mononuclear cells obtained from men with AIDS or its prodrome were capable of depressing T-helper cell-dependent immune reactivity (30). It appears that the defect lies within the T-cell which produces the factor that, in turn, inhibits monocyte recognition of the antigens. Characterization of this lymphokine has been aided by the development of T-lymphocyte hybridomas from an ARC patient. SSF is a protein of about 47,000 dalton which can induce an immunodeficiency state in mice. This may prove to be a valuable animal model to study the pathogenesis of AIDS. AIDS patients also lacked the ability to generate gamma interferon (g-IFN), a macrophage activating factor produced by T-lymphocytes. The antimicrobial function of their macrophages was intact and functional in the presence of exogenous g-IFN in vitro. Homosexual men with lymphadenopathy alone had normal g-IFN production. On the other hand, if lymphadenopathy was concurrent with additional symptoms such as prolonged oral thrush, fever, or weight loss, there was an impairment of g-IFN production. It appears that the primary defect in the production of g-IFN by these patients lay in the ability of their lymphocytes to recognize and respond to specific antigens.

In another project (66), an additional defect in lymphokine production was noted in the ability of AIDS patients with opportunistic infections (OI) to produce interleukin-2 (IL-2), a factor stimulating T-cell proliferation. This defect was less marked in KS-AIDS patients and in some lymphadenopathy patients. Hemophiliacs whose helper to suppressor cell ratios and T-cell proliferation assay values were in the lower limits of normal for the control population had normal g-IFN and IL-2 production. Taken together, these data indicate that a gradient of immune pathology exists from hemophilia to lymphadenopathy, KS-AIDS, and finally OI-AIDS. These populations are being followed prospectively to identify immunologic abnormalities that indicate significant risk for development of AIDS in order to propose methods for therapeutic intervention.

Another aspect of AIDS activity being supported by this Branch is the investigation of risk factors for AIDS in Haitian communities, both in Miami (35) and in Haiti (30). Two case-control studies are in progress. They have required the full

cooperation of the communities to develop epidemiologic instruments reflecting the linguistic and cultural characteristics of the Haitians. The importance of these projects lies in the observation that the risk factors for Haitians appear to be different than those for the U.S. homosexual men. In Haiti, bisexuality (43%) is the most common risk factor in males, and blood transfusions (41%) most common in female AIDS patients. No risk factors have been identified for 52% of the cases.

Patients with AIDS in Haiti come from all strata of society. Recent testing for HTLV-III antibody in Haiti indicates its presence in 93% of AIDS patients, in 11% of their siblings and friends, and in 60% of the heterosexual partners of the AIDS patients (63% of female partners of male AIDS patients and 60% of the male partners of female cases were HTLV-III antibody positive). None of the healthy heterosexual hospital staff tested in Haiti were seropositive for HTLV-III. Heterosexual transmission may play an important role in Haiti; 82% of male patients had multiple heterosexual partners (median of 24) versus 35% of healthy control males, and 24% of female AIDS cases had multiple heterosexual partners versus none of their controls. Similar patterns of spread are being seen within the Haitian community in Miami (35). Transmission of HTLV-III in this population is often blood-borne via blood transfusions of unscreened blood or contaminated needles used in the administration of injectable medications by non-medical practitioners.

The occurrence of AIDS in Haitian infants suggests congenital or in utero transmission. AIDS or ARC, as well as HTLV-III seropositivity, are more common in younger children (less than 2 years of age) whose mothers have symptoms or are seropositive (30, 35). Transmission of infection is likely to be transplacental, based upon the very young age at which the disease develops in the offspring and by the lack of association with paternal status or of transmission to older siblings. Furthermore, mothers can have subsequent pregnancies with infected offspring, indicating a prolonged period of maternal infectivity. This Branch sponsored a conference on Pediatric AIDS in November 1984 (98), and hopes to further stimulate research efforts directed towards this problem.

Another important area of concern to this Branch is the potential for an increased incidence of malignant lymphomas and other cancers in groups at high risk for AIDS. Data indicate that among the groups that are at high risk of developing frank AIDS, there are asymptomatic subgroups with evidence of disturbances of immunoregulatory mechanisms, as reflected by numbers, phenotypes, and functions of lymphocytes. It is possible that individuals with this epidemic form of immunosuppression will be at an increased risk of additional malignancies, notably non-Hodgkin's lymphoma, which occur in individuals who are congenitally or medically immunosuppressed. A recent report studied the relationship between non-Hodgkin's lymphoma and AIDS in 90 homosexual men, concluding that this lymphoma in this risk group should be included as a manifestation of AIDS or the AIDS-related complex. This Branch is supporting several epidemiologic studies aimed at documenting the increased incidence of malignancies associated with the AIDS epidemic and the elucidation of the relevant etiologic factors (26, 58, 60, 75, 101). Early results support the linkage between the AIDS epidemic and an increase in lymphomas and anorectal carcinomas in homosexual men.

A cohort of homosexual men with biopsy-proven reactive lymphadenopathy--a syndrome of persistent generalized lymphadenopathy (PGL) in the absence of any known intercurrent disease--is being followed, as are controls who are asymptomatic male homosexuals living in the same neighborhood, age-matched, and who do not share intimate sexual relations with the case (75). HTLV-III antibody seropositivity

is 96% (49/51) in the cases and 55% (17/31) in the controls. HTLV-III virus has been isolated from lymph node tissue of 46% of the cases. One of the cases has evolved from PGL to malignant B-cell lymphoma within the first 9 months of the study. Within Los Angeles County, there has been a significant increased incidence of B-cell immunoblastic sarcoma and small non-cleaved lymphoma (Burkitt or Burkitt-like) since 1981 in never married males (ages 18-54 years): 4% of all non-Hodgkin's lymphomas in 1972-79 vs. 20% in 1980-83, contrasted to 3% and 4%, respectively, in same aged married men. Furthermore, HTLV-III antibodies have been detected in 88% (15/17) of sera from homosexual men currently with this high-grade lymphoma, significantly more than the 40% (2/5) prevalence found in male homosexuals with low grade (small-cleaved or plasmacytoid lymphocytic) lymphomas. Occurrence of lymphomas in unusual extra-nodal sites, such as the central nervous system or rectum, is another distinguishing feature of these retrovirus-associated lymphomas.

Projections: Epidemiologic studies have identified groups at high risk for AIDS. The preponderance of the data has arisen from the homosexual male population, as they represent the majority of cases and are potentially more accessible than the intravenous drug abusers or the new Haitian immigrants. However, there are differences in the manifestations of the disease in the various risk groups, such as the greater percentage of KS in homosexual men, that need continued and further study to delineate their etiologies. What are the contributing roles of sexual practices, routes of entry of antigens (infections and alloantigens), antigen overloads, and genetic constitutions? Of vital import is the need to establish whether HTLV-III is necessary but not sufficient, needing some co-factor for the expression of disease. In addition to the need for more information on the epidemiology of AIDS in Haitians, there is the need to study the African connection. In addition to transmission of AIDS by blood and blood products, it is necessary to study the transmission of AIDS from parents to children. Furthermore, it is becoming clearer that the spectrum of AIDS is broader than the initial CDC case definition. The association of AIDS with lymphomas is not only biologically plausible, it appears to exist.

Research on AIDS and AIDS-related diseases should not be too narrowly focused upon HTLV-III. As with many viruses, infection may be necessary but not sufficient for the production of disease. The massive research effort directed towards AIDS should produce a much better understanding of the intimate interrelationships between the infective agent and the host.

NUTRITION-RELATED EPIDEMIOLOGY

Description: Epidemiological observations and studies in laboratory animals suggest that diet, as an etiologic factor distinct from dietary contaminants and from genetic and environmental factors, plays a role in the causation of some forms of human cancer.

Diet could influence cancer in several ways: through undernutrition; by affecting the immune system; through carcinogens as contaminants of food; through the formation of carcinogens produced in vivo from ingested food; through the formation of carcinogens during the storage, processing or cooking of foods; and through the protective effect of certain dietary components by their influence on the carcinogen detoxification systems.

It is conceivable that, due to complex interactions, dietary factors may protect against cancer in one organ, but induce cancer in another. This phenomenon has

been observed in animal studies in which ascorbic acid inhibited tumor formation in the liver but induced it in the forestomach. Likewise, in case-control studies, a diet rich in ascorbic acid was associated with reduced risk of cancer of the oral cavity, larynx and esophagus but not of the stomach or rectum (44).

Research Accomplishments: In a recently completed case-control study among the multiethnic population of Hawaii, it was found that total vitamin A intake (food sources plus supplements), vitamin A intake from food sources only, and carotene intake (but not ascorbic acid intake) were each inversely associated with lung cancer risk in males only. A possible explanation for the differential effect with respect to sex may be the different distribution of lung cancer histologies in men and women - epidermoid cancer being more common in men and adenocarcinoma in women (67).

Over eight thousand Japanese men residing in Hawaii, aged 45-68, were examined between 1965 and 1968 and were followed for 15 years. It was found that body mass index (BMI) at time of examination, and weight gain since age 25, were positively associated with an increased risk of colon cancer in men age 55 or older at the time of examination. No other cancer had a significant positive association with either of these indices. A low BMI at examination and weight loss since age 25, however, were associated with an increased risk of stomach cancer; only weight loss since age 25 was associated with an increased risk of lung cancer (94).

The original objective of an ongoing population-based study in the People's Republic of China was to correlate site-specific cancer mortality rates with selenium nutritional status. This study has now been expanded so that cancer mortality could be examined with respect to multiple dietary/nutritional factors. It is hoped that the data will permit evaluation of the relative contribution of individual factors and will permit assessment of the importance of interactions (17).

The ongoing study of Seventh-Day Adventists (SDA) was designed to identify specific elements of lifestyle that relate to cancer risk within the SDA population and to identify interactions among various lifestyle factors. In this study, overweight men had a risk for fatal cancer of 2-5 times that for men near their desirable weight. There was also a suggestive positive association with intake of milk, cheese, eggs and meat. Although the relationship between the intake of any individual animal product and fatal prostate cancer was weak, the combined heavy consumption of all four animal products had an estimated relative risk of 3-6. There may be some systematic bias related to the sole use of mortality as an end point in this study, which needs further exploration (103). A significant negative association with green salad intake, and a significant positive association with meat and egg consumption by the Seventh-Day Adventists, was observed when data from a self-administered food questionnaire for 28 specific foods were analyzed for mortality from all causes (103).

In an ongoing study of Colombian subjects, urinary excretion of sodium was measured to test the hypothesis that excessive intake of sodium chloride might be a risk factor for gastric cancer. It was found that Colombians living in a high risk area excreted greater amounts of urinary sodium than those living in a low risk area. This observation is in agreement with several published studies which have consistently reported an elevated risk of gastric cancer associated with the ingestion of salted foods (23).

To investigate the association of dietary vitamin D and calcium with colon cancer risk, 1954 men (aged 40-55 years) who had completed detailed dietary diaries at the time of the baseline examination in 1957-59 were followed for 19 years. Risk of colorectal cancer was found to be inversely correlated with dietary vitamin D and calcium in this study group. This association remained significant even after adjustment for age, smoking, body mass index, alcohol consumption, and percentage of calories from dietary fat (115).

Projections: In order to encourage research designed to identify, characterize and validate markers of present or past dietary intake which could be useful in the conduct of nutritionally focused studies in cancer epidemiology, an RFA was issued in May 1984. Only six applications were received in response to this announcement. Of the four applications recommended for approval, not a single application received a fundable priority score. Advice of the Division's Board of Scientific Counselors will be sought in order to explore ways to stimulate research in this area.

TOBACCO-RELATED EPIDEMIOLOGY

Description: The Extramural Smoking and Health Program in the Division of Cancer Etiology is involved in efforts to understand and mitigate the deleterious effects of smoking on health. This Branch supports only epidemiological investigations designed to determine the effects of tobacco products on cancer risk.

Research Accomplishments: The dramatic increase in lung cancer incidence and mortality rates among women in recent years have been attributed to increased cigarette smoking. A recently initiated case-control study is attempting to assess the effects of a variety of factors on lung cancer risk by histologic type. These factors include: reproductive and hormonal status; occupational exposures; interaction of dietary factors with smoking and occupational risk factors; passive smoking and air pollution (122).

An ongoing prospective study seeks to determine if smoking cigarettes with a relatively low yield of tar and nicotine (tar <15 mg and nicotine <1.0 mg per cigarette) is less hazardous than smoking cigarettes with a higher yield of tar and nicotine (39).

A multidisciplinary study is continuing to explore the relationship of smoking with a variety of cancers in populations who have switched to smoking low-yield cigarettes. By developing a new sensitive radioimmunoassay for nicotine metabolites, an attempt will be made to explain how heavy smokers adapt to low-yield cigarettes. A subproject seeks to determine if lung cancer in nonsmokers is associated with exposure to sidestream tobacco smoke. Validation of self-reported exposure to passive inhalation of tobacco smoke will be carried out biochemically through the use of radioimmunoassay for cotinine in biological fluids. Another subproject is testing the hypothesis that alcohol may interfere with the metabolic detoxification of carcinogens which occur in cigarette smoke (155).

Projection: Tobacco smoke is probably one of the most ubiquitous indoor pollutants in the world. In recent years some epidemiological studies have indicated an association between involuntary smoking and an increased risk of lung cancer. The pattern of involuntary inhalation of tobacco smoke is probably different from that of voluntary inhalation by the smoker. The question, therefore, arises whether a

person exposed involuntarily for many years to the smoke of others inhales sufficient amounts of carcinogens to elicit a carcinogenic response. An RFA was published in June 1984 to stimulate additional research to assess the effect of involuntary exposure to tobacco smoke on cancer risk. Applications responding to this announcement were recently reviewed by a special study section. Although a funding decision has not yet been made, some of the applications will be funded during this fiscal year.

BIOCHEMICAL EPIDEMIOLOGY

Description: A significant portion of human cancers are thought to be attributable to lifestyle and other environmental factors and are, therefore, potentially preventable. The process of induction and progression of human cancer is exceedingly complex. Epidemiologic studies have identified factors which appear to increase or decrease cancer risk and have suggested the importance of host susceptibility factors. The usual epidemiologic techniques, however, have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states; in measuring low levels of risk; in evaluating directly host-environmental interactions; and in identifying dietary determinants of cancer. Recent development of a variety of sensitive and specific laboratory methods should facilitate epidemiologic investigations by providing better measures of exposure. In order to foster collaboration between laboratory scientists and epidemiologists in the application of these emerging techniques, a program in biochemical epidemiology was initiated in 1982.

Issuance of a request for applications in the area of biochemical epidemiology resulted in the funding of 14 grants in fiscal year 1983. These studies are taking advantage of a variety of laboratory procedures focusing on such factors as DNA damage and repair capacity, chromosomal changes, diet and nutrition, and selected viral exposures. A few of the ongoing studies are highlighted below.

Research Accomplishments: Cancers of the biliary tract provide a unique opportunity to combine epidemiological and biochemical approaches to elucidate the etiology of these cancers which are uncommon in the United States but are of considerable international importance. Although the entire biliary tract is bathed in the same material, namely bile, there are significant differences in the epidemiology of cancers of the different parts of the biliary tract. Moreover, there are marked differences in the incidence of these diseases between countries. Through an ongoing case-control study in Mexico and Bolivia, attempts are being made to determine whether patients with different primary cancers of the biliary tract differ from each other, from patients with cholelithiasis, and from patients with other abdominal illnesses. Data are being collected on familial aggregation, demographic characteristics, environmental exposures and number of biochemical parameters such as serum cholesterol, gallstone composition, bile and serum levels of carcinoembryonic antigen, and conjugates of bile acids and lithocholic acid in the bile and serum (123). Development of an immunoassay for benzo(a)pyrene bound to DNA as a measure of biologically effective dose of the carcinogen is underway in a second study (140). The method is being evaluated for its potential to serve as a quantitative indicator of increased risk of lung cancer.

There are strong indications that genetic instability is one of the predisposing factors for human cancer. It has been suggested that genetic instability may be widespread in the human population and may be the cause of a variety of neoplastic diseases. An ongoing study is evaluating cytogenetic screening for chromosome

damage as a test for predicting diseases in humans. If it is possible to differentiate between stable and unstable genomes by challenging cultured lymphocytes with chromosome damaging agents, it would be possible to screen human families/populations and study the relationship between sensitivity to clastogens and risk for development of cancer. This screen would provide a potent prognostic tool to differentiate persons with a very high genetic stability and those who are less stable (61).

The etiology of vulvar cancer is poorly understood. Through a partly retrospective and partly prospective approach, a recently initiated study is attempting to determine if infection with a sexually transmitted virus is related to an increased risk of vulvar cancer. In this study, if the presence of a specific gene product in neoplastic cells of vulvar carcinomas, but not in normal cells from the same subject or in normal cells of subjects with benign pigmented nevi of the vulva, can be demonstrated, it would be persuasive of a specific viral association (27).

Projection: The response to the first announcement for research in biochemical epidemiology was excellent. In order to further encourage collaborative studies between epidemiologists and laboratory scientists, the RFA was reissued in December 1983. Thirty two applications responding to this announcement were reviewed by a special study section. Of the eighteen applications recommended for approval, only three applications were judged to be sufficiently meritorious for funding.

It is planned to issue in the near future an announcement for cooperative agreements to encourage investigations designed to develop, characterize, validate and apply laboratory-based biological markers of human exposure which would be useful in the conduct of epidemiologic studies.

EXTRAMURAL PROGRAMS BRANCH

GRANTS ACTIVE DURING FY 85

	Investigator/Institution/Grant Number	Title
1.	ADAMI, Hans-Olov University of Uppsala 1 R01 CA 40264-01	The Risk for Gastric Cancer After Partial Gastrectomy
2.	ALLEN, Arline M. Northwestern University 5 R01 CA 35943-02	Validation of Long-Term Dietary Recall
3.	ASAL, Nabih R. University of Oklahoma Hlth. Sci. Ctr. 2 R01 CA 31059-04	Risk Factors in Renal Cell Carcinoma
4.	AUSTIN, Harland D. University of Alabama (Birmingham) 1 R01 CA 39733-01	Case-Control Study of Endometrial Cancer and Obesity
5.	AWERBACH, Tamara E. Harvard University 1 R23 CA 37820-01	Mathematics of Diffusion Assays--Mutagens & Antibiotics
6.	BEASLEY, R. Palmer University of Washington 5 R01 CA 25327-06	Hepatocellular Carcinoma Risk in Hepatitis B Carriers
7.	BEGG, Colin B. Dana-Farber Cancer Institute 5 R01 CA 35291-02	Treatment Allocation in Sequential Clinical Trials
8.	BISHOP, David T. University of Utah 5 R23 CA 36362-02	Linkage Analysis and Multiple Loci
9.	BLUMBERG, Baruch Institute for Cancer Research 7 P01 CA 40737-01	Cancer Clinical Research at the Fox Chase Center - HBV and PHC
10.	BRADLOW, H. Leon Rockefeller University 1 R01 CA 39734-01	Obesity, Diet, Estrogens and Cancer Risk
11.	BRANDSMA, Janet L. Long Island Jewish-Hillside Med. Ctr. 1 R01 CA 39172-01	Cancers of the Head and Neck: Epidemiology and Biochemistry
12.	BRESLOW, Norman E. University of Washington 1 R01 CA 40644-01	Statistical Methods in Cancer Epidemiology

13. BUFFLER, Patricia A.
University of Texas Hlth. Sci. Ctr.
5 R01 CA 32584-03
CNS Tumors and Occupational Exposures

14. BUFFLER, Patricia A.
University of Texas Hlth. Sci. Ctr.
5 R01 CA 34448-02
Occupational and Environmental Exposures in the Etiology of Adult Leukemia

15. BUZZARD, I. Marilyn
University of Minnesota (Mnpls-St Paul)
5 R01 CA 36522-02
Microcomputer-Based Dietary Data Collection Systems

16. BYERS, Tim
State University of New York (Buffalo)
5 R01 CA 35903-02
Reliability of Dietary History Based on Distant Recall

17. CAMPBELL, T. Colin
Cornell University (Ithaca)
5 P01 CA 33638-02
Dietary Selenium and Cancer

18. CASAGRANDE, John T.
University of Southern California
5 R01 CA 27829-02
An Epidemiologic Study of Male Breast Cancer

19. COLE, Philip
University of Alabama (Birmingham)
5 R01 CA 29968-03
Hepatocellular Carcinoma and Cigarette Smoking

20. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 35917-02
Vitamin A, Vitamin E, Selenium and Colon Cancer Risk

21. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 35918-02
Biochemical Markers of Nutrition and Lung Cancer

22. COMSTOCK, George W.
Johns Hopkins University
1 R01 CA 36390-01
Serologic Precursors of Cancer

23. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
5 P01 CA 28842-04
Etiologic Studies of Gastric Carcinoma

24. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
1 R01 CA 40095-01
Lung Cancer in Non-Smoking Women

25. CRAMER, David W.
Brigham and Women's Hospital
1 R01 CA 38032-01
Correlates of Ovarian Cancer Risks

26.	DALING, Janet R. University of Washington 5 R01 CA 32010-04	Epidemiology of Anal Cancer
27.	DALING, Janet R. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 35881-02	Vulvar Cancer--Epidemiology, Biochemistry and Immunology
28.	DE METS, David L. University of Wisconsin (Madison) 2 R01 CA 18332-10	Statistical Problems in Cancer Research
29.	DE ROUEN, Timothy University of Washington 5 R01 CA 34493-02	Etiology and Natural History of Cervical Neoplasia
30.	DOUGLAS, R. Gordon Cornell University Med. Ctr. 5 U01 CA 35018-03	Collaborative Studies of AID/Kaposi's Sarcoma
31.	DWYER, Johann T. Harvard University 5 R01 CA 35939-02	Accuracy of Historic Dietary Data from Questionnaire
32.	ELSTON, Robert C. Louisiana State Univ. Med. Ctr. 2 R01 CA 28198-06	Statistical Genetic Analysis for Cancer Families
33.	EVANS, Alfred S. Yale University 2 R01 CA 30433-03A1	Epidemiological Studies of EBV in Hodgkin's Disease
34.	FIALKOW, Philip J. University of Washington 2 R01 CA 16448-11	Human Cancer -- Origin and Genetic Markers
35.	FISCHL, Margaret A. University of Miami 5 U01 CA 34988-02	A Study of an Acquired Immunodeficiency Syndrome
36.	FOLSOM, Aaron R. University of Minnesota 1 R01 CA 39742-01	Distribution of Body Fat and Cancer Risk in Women
37.	FOX, C. Fred University of California (Los Angeles) 1 R13 CA 39223-01	Conference on Biochemical and Molecular Epidemiology of Cancer
38.	FRIEDMAN, Gary D. Kaiser Foundation Res. Inst. 5 R01 CA 19939-09	Surveillance for Drugs That May be Carcinogenic
39.	FRIEDMAN, Gary D. Kaiser Foundation Res. Inst. 1 R01 CA 36074-01A1	Are Low-Yield Cigarettes Less Hazardous?

40. GERMAN, James L.
New York Blood Center
5 R01 CA 38036-02
Maintenance of the Bloom's Syndrome Registry

41. GIESE, Roger W.
Northeastern University
5 R01 CA 35843-02
Ultratrace Analysis of DNA Lesions with Electrophoresis

42. GOLD, Ellen B.
Johns Hopkins University
5 R01 CA 35859-02
Biochemical Markers for Lung Cancer in a High Risk Group

43. GORBACH, Sherwoood L.
New England Med. Ctr. Hospitals, Inc.
5 R01 CA 35840-02
Diet, Estrogens, and Breast Cancer

44. GRAHAM, Saxon
State University of New York (Buffalo)
5 P01 CA 11535-14
Social Epidemiology of Cancer

45. GRIFFIN, Marie
Mayo Foundation
5 R01 CA 36396-02
Cancer Risk in Patients with Thrombotic Episodes

46. GRUFFERMAN, Seymour
Duke University
5 R01 ca 21244-05
The Epidemiology of Childhood Rhabdomyosarcoma

47. GUTENSOHN, Nancy M.
Harvard University
5 R01 CA 31747-03
Hodgkin's Disease and Pre-Diagnostic EBV-Antibody Status

48. GUTENSOHN, Nancy M.
Harvard University
1 R01 CA 38450-01
Risk Factors for Human T-Cell Leukemia Virus Infection

49. HAENSZEL, William M.
Illinois Cancer Council
5 R01 CA 34044-03
Cholecystectomy and Subsite-Specific Large Bowel Cancer

50. HANASH, Samir M.
University of Michigan (Ann Arbor)
5 P01 CA 26803-06
Program Project: The Study of Human Mutation

51. HARRINGTON, David P.
Dana-Farber Cancer Institute
7 R01 CA 39929-01
Nonparametric Statistical Tests for Censored Cancer Data

52. HENDERSON, Brian E.
University of Southern California
5 P01 CA 17054-10
USC Cancer Center Epidemiology and Biostatistics Unit

53. HENDERSON, Brian E.
University of Southern California
5 R01 CA 32197-04
The Role of Estrogens and Vitamin A in Disease Prevention

54.	HERBST, Arthur L. University of Chicago 5 R01 CA 32012-03	Cancer and Health Risks in DES Exposed Daughters
55.	HILDRETH, Nancy G. University of Rochester 2 R01 CA 19764-07A1	Human Radiation Carcinogenesis Study
56.	HOFFMANN, Dietrich American Health Foundation 1 R01 CA 40070-01	Biochemical Validation of Smoke Absorption by Infants
57.	HOLLY, Elizabeth A. Northern California Cancer Program 5 R01 CA 34382-02	Melanoma, Oral Contraceptives Use and Reproductive Factors
58.	HOLLY, Elizabeth A. Northern California Cancer Program 5 R01 CA 35676-02	Epidemiology: Ewing's Sarcoma, Anal and Rectal Carcinoma
59.	HOLLY, Elizabeth A. Northern California Cancer Program 5 R01 CA 37950-02	Epidemiology of Ocular Melanoma
60.	HOLMES, Frederick F. University of Kansas Col. Hlth. Sci. 5 R01 CA 35683-02	Anal Cancer in Women: Etiologic Factors
61.	HSU, T.C. University of Texas System Cancer Ctr. 5 R01 CA 35007-02	Cytogenetic Assays of Human Genetic Instability
62.	HULKA, Barbara S. University of North Carolina 5 R01 CA 35915-02	Hormone Receptors and Serum Assays in Prostatic Cancer
63.	HUTCHISON, George B. Harvard University 5 R01 CA 22849-08	Second Cancers in Patients with Hodgkin's Disease
64.	HUTCHISON, George B. Harvard University 1 R01 CA 38071-01	Epidemiology of Non-Hodgkin's Lymphoma
65.	JANERICH, Dwight T. New York State Dept. of Health 5 R01 CA 32088-04	Epidemiology of Lung Cancer in Nonsmokers
66.	KIRKPATRICK, Charles H. National Jewish Hosp. & Res. Ctr. 5 U01 CA 35006-02	Pathogenesis of Acquired Immune Deficiency Syndrome
67.	KOLONEL, Laurence N. University of Hawaii (Manoa) 5 P01 CA 33619-03	Epidemiologic Studies of Diet and Cancer in Hawaii

68. KOZIOL, James A.
University of California (San Diego)
2 R01 CA 26666-07
Topics in Biostatistics

69. KREGER, Bernard E.
Boston University
1 R01 CA 39766-01
Obesity and Cancer Risk in Women

70. KUZMA, Ian W.
Loma Linda University
5 R01 CA 35888-02
Long-Term Dietary Recall of Cancer Cases

71. LACHENBRUCH, Peter A.
University of Iowa
5 R01 CA 24089-06
Estimation of Prognosis Using SEER Data

72. LAGAKOS, Stephen W.
Harvard University
2 R01 CA 33041-04
Biostatistical Methods for Carcinogenicity Experiments

73. LAGAKOS, Stephen W.
Dana-Farber Cancer Institute
1 R01 CA 39640-01
Biostatistical Problems in Cancer Research

74. LEE, Ilbok
Biostatistical Services, Inc.
1 R43 CA 37533-01
Evaluation of Reliability Growth Models

75. LEVINE, Alexandra M.
University of Southern California
5 R01 CA 36301-02
Epidemiology and Immunology in Homosexuals with PGL

76. MACK, Thomas M.
University of Southern California
5 R01 CA 23927-05
Case-Control Study of Malignant Melanoma

77. MACK, Thomas M.
University of Southern California
5 R01 CA 32262-03
Determinants of Cancer within Disease-Discordant Twins

78. MACMAHON, Brian
Harvard University
3 P01 CA 06373-22S1
Cancer Epidemiology and Prevention Research Center

79. MACMAHON, Brian
Harvard University
5 R01 CA 29723-04
An Epidemiologic Study of Renal Adenocarcinoma

80. MARMOR, Michael
New York University
5 R01 CA 33205-03
Risk Factors for Kaposi's Sarcoma in Homosexual Men

81. MASHBERG, Arthur
University of Med. & Dent. (New Jersey)
2 R01 CA 29214-03
Role of Alcohol as a Primary Risk Factor in Oral Cancer

82.	MATANOSKI, Genevieve M. Johns Hopkins University 1 R01 CA 39764-01	Body Fat Distribution Type as an Endometrial Cancer Risk
83.	MEADOWS, Anna Children's Hospital (Philadelphia) 2 R01 CA 29275-04	Etiologic Factors Related to Childhood (Embryonal) Tumor
84.	MEADOWS, Anna Children's Hospital (Philadelphia) 5 R01 CA 36222-02	An Epidemiologic and Cytogenetic Study of Retinoblastoma
85.	MEHTA, Cyrus R. Dana-Farber Cancer Institute 5 R01 CA 33019-04	Statistical Methods for Cancer Treatment and Prevention
86.	MENCK, Herman R. University of Southern California 5 R01 CA 35477-02	Case-Control Study of Gall Bladder Cancer
87.	MILLER, Kenneth J. Rensselaer Polytechnic Institute 5 R01 CA 28924-03	Computer Assisted Analysis of Carcinogenicity
88.	MOOLGAVKAR, Suresh H. Fred Hutchinson Cancer Res. Ctr. 7 R01 CA 39948-01	Malignant Melanoma Mutifactoral and Stochastic Models
89.	MOOLGAVKAR, Suresh H. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 39949-02	Biomathematical Approaches to Cancer
90.	MORGAN, Timothy M. Wake Forest University 1 R23 CA 39575-01	Efficiency of Covariate Adjustment in the Cox Model
91.	NEWELL, Guy R. University of Texas System Cancer Ctr. 5 R01 CA 34048-03	Nutrition Methodology for Epidemiological Cancer Studies
92.	NICHOLS, Warren W. Institute for Medical Research 5 P01 CA 33624-03	Epidemiologic/Lab Investigation of Cancer-Prone Children
93.	NIELSON, Kirk K. Rogers & Assoc. Engineering Corp. 1 R43 CA 38519-01	Dietary Mineral Assessment in Cancer Epidemiology
94.	NOMURA, Abraham M. Kuakini Medical Center 5 R01 CA 33644-02	Cancer Epidemiology of the Migrant Japanese in Hawaii
95.	OLSHEN, Richard A. University of California (San Diego) 1 R01 CA 41628-01	Biostatistics: Modeling and Inference

96. PAFFENBARGER, Ralph S.
Stanford University
5 R01 CA 25264-05
Early Predictors of Site-Specific Cancers

97. PAFFENBARGER, Ralph S.
Stanford University
5 R01 CA 35067-02
Etiologic Factors for Epithelial Ovarian Cancer

98. PARKS, Wade P.
University of Miami
1 R13 CA 39968-01
Conference to Define AIDS in Pediatric Patients

99. PERERA, Frederica P.
Columbia University (New York)
1 R01 CA 39174-01
Carcinogen Dosimetry and Oncogene Activation in Human Subjects

100. PERSKY, Victoria W.
Northwestern University
1 R01 CA 37297-01
Serum Hormones in Vegetarian and Non-Vegetarian Girls

101. PETERS, Ruth K.
University of Southern California
5 R01 CA 35706-02
Epidemiology of Epithelial Tumors of the Anogenital Area

102. PETERS, Ruth K.
University of Southern California
1 R01 CA 36501-01A1
Case Control Study of Colon Carcinoma

103. PHILLIPS, Roland L.
Loma Linda University
5 R01 CA 14703-12
Epidemiology of Cancer in Adventists--a Low Risk Group

104. PIERCE, Donald A.
Oregon State University
5 R01 CA 27532-05
Statistical Methodology for Response-Time Data

105. PIZER, Lewis I.
University of Colorado Hlth. Sci. Ctr.
5 R01 CA 35906-02
HSV-Markers and the Epidemiology of Cervical Cancer

106. PRENTICE, Ross
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 32913-03
Statistical Methods for Medical Data

107. PRESTON-MARTIN, Susan
University of Southern California
5 R01 CA 28215-06
Epidemiology of Tumors of the Parotid Gland

108. RACHLIN, Jean K.
Frontier Science Associates, Inc.
1 R43 CA 36681-01A1
Statistical Software for Analysis of Categorical Data

109. ROBISON, Leslie L.
University of Minnesota (Mnpls-St Paul)
5 R23 CA 35314-02
Epidemiology Study of Childhood Acute Leukemia

110. ROBISON, Leslie L.
University of Minnesota (Mnpls-St Paul)
5 R01 CA 35488-02
Epidemiologic Study of Ewing's Sarcoma

111. ROSS, Ronald K.
University of Southern California
1 R01 CA 36388-01A2
Case-Control Study of Multiple Myeloma

112. ROTHMAN, Kenneth J.
University of Massachusetts Med. Sch.
5 R01 CA 38455-02
Case-Control Study of Laryngeal-Hypopharyngeal Cancer

113. SAFAI, Bijan
Memorial Hosp. for Cancer & Allied Dis.
5 R01 CA 34822-02
Epidemiology: Kaposi Sarcoma and Acquired Immune Deficiency

114. SAMET, Jonathan M.
University of New Mexico (Albuquerque)
5 R01 CA 27187-05
Lung Cancer Etiology in Hispanics and Anglos

115. SHEKELLE, Richard B.
University of Texas Hlth. Sci. Ctr.
5 R01 CA 38326-02
Diet, Alcohol, Tobacco and Risk of Cancer in Men

116. SHULTZ, Terry D.
Loma Linda University
5 R23 CA 36008-02
Diet Hormone Metabolism and Breast Cancer Risks

117. SHY, Carl
University of North Carolina
1 R13 CA 37134-01
Silica, Silicosis and Cancer--An International Symposium

118. SKOLNICK, Mark H.
University of Utah
5 R01 CA 28854-05
Genetic Epidemiology of Cancer in Utah Genealogies

119. SPEIZER, Frank E.
Peter Bent Brigham Hospital
5 R01 CA 26560-06
Prospective Study of Diet and Cancer in Women

120. SPEIZER, Frank E.
Peter Bent Brigham Hospital
7 R01 CA 40935-01
Epidemiology of Diet and Cancer in Women

121. STEBBINGS, James H.
University of Chicago
1 R01 CA 40071-01
Dose Interactions of Passive Smoking with Domestic Radon

122. STEMHAGEN, Annette
New Jersey State Dept. of Health
1 R01 CA 37744-01
Epidemiology of Lung Cancer Among Women in New Jersey

123. STROM, Brian L.
University of Pennsylvania
5 R01 CA 35934-02
Biochemical Epidemiology of Biliary Tract Cancer

124. STRONG, Louise C.
University of Texas System Cancer Ctr.
2 R01 CA 27925-04
Genetic Etiology and Consequences of Childhood Cancer

125. STRONG, Louise C.
University of Texas System Cancer Ctr.
5 R01 CA 32064-03
Identification of Genes Predisposing to Childhood Cancer

126. STRONG, Louise C.
University of Texas System Cancer Ctr.
1 R01 CA 38929-01
Genetic Epidemiology of Childhood Sarcoma

127. SWIFT, Michael R.
University of North Carolina
5 R01 CA 14235-12
Neoplasia-Predisposing Genes of Man

128. SZKLO, Moyses
Johns Hopkins University
5 R01 CA 26500-05
Epidemiologic and HLA Study of Leukemia

129. SZKLO, Moyses
Johns Hopkins University
5 R01 CA 33822-02
Epidemiologic and Immunogenetic Study of Macroglobulinemia

130. TANNER, Martin A.
University of Wisconsin (Madison)
1 R23 CA 35464-01A1
Nonparametric Analysis of Censored Data

131. TARTER, Michael E.
West Coast Cancer Foundation
5 R01 CA 28142-03
Modern Functional Representation in Cancer Research

132. TARTER, Michael E.
West Coast Cancer Foundation
5 R01 CA 35795-02
Nonparametric Estimation of Cancer Dose Response Curves

133. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 30022-02
Alcohol and Cancers of the Larynx and Esophagus

134. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 35653-02
Epidemiology of Male Breast Cancer

135. THOMPSON, W. Douglas
Yale University
1 R01 CA 39477-01
An Epidemiologic Study of Multiple Primary Breast Cancer

136. TSIATIS, Anastasios A.
Dana-Farber Cancer Institute
5 R01 CA 36446-02
Early Stopping of Clinical Trials

137. TSUTAKAWA, Robert K.
University of Missouri (Columbia)
5 R01 CA 29765-03
Statistical Analysis of Cancer Mortality Rates

138. WALLACE, Robert B.
University of Iowa
5 R01 CA 35818-02
Carcinogen-Metabolizing Enzymes and Cancer Risk

139. WEI, Lee-Jen
George Washington University
1 R01 CA 38383-01
Biostatistical Inference Problems

140. WEINSTEIN, I. Bernard
Columbia University (New York)
5 R01 CA 35809-02
Molecular Cancer Epidemiology: BAP-DNA Binding

141. WEISS, Kenneth M.
University of Texas Hlth. Sci. Ctr.
5 R01 CA 19311-07
Genetic Epidemiology of Cancer

142. WEISS, Noel S.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 35679-02
The Epidemiology of Multiple Myeloma

143. WEISS, Noel S.
University of Washington
1 R35 CA 39779-01
Research in Cancer Epidemiology

144. WEST, Dee W.
University of Utah
5 P01 CA 34243-02
Epidemiologic and Biochemical Studies of Nutrition

145. WEST, Dee W.
University of Utah
1 R01 CA 40060-01
Passive Smoking as a Cervical Cancer Risk Factor

146. WHITE, Colin
Yale University
5 R01 CA 30931-04
Systematic Analysis--Connecticut Cancer Incidence Trends

147. WHITTEMORE, Alice S.
Stanford University
2 R01 CA 23214-07
Effects of Multiple Exposures: Quantitative Aspects

148. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 33940-02
Reliability of Long-Term Dietary Recall

149. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 35208-02
Etiologic Factors for Mycosis Fungoides

150. WHITTEMORE, Alice S.
Stanford University
5 R01 CA 36503-02
Colo-Rectal Cancer in Chinese and Chinese-Americans

151. WILLETT, Walter L.
Brigham and Women's Hospital
2 R01 CA 33008-04
A Cohort Study of Trace Elements and Cancer in Women

152.	WILLETT, Walter L. Harvard University 5 R01 CA 35837-02	Carotene, Vitamins A and E, and Risk of Melanoma
153.	WILLIAMS, Jerry R. Johns Hopkins University 7 R01 CA 39654-01	Cellular Markers of Cancer Risk in PUVA-Treated Humans
154.	WOODS, James S. Battelle Memorial Institute (Seattle) 5 R01 CA 29900-03	Cancer Incidence and Phenoxy Herbicide Exposure
155.	WYNDER, Ernst L. American Health Foundation 2 P01 CA 32617-04	Interdisciplinary Studies in Cancer Epidemiology
156.	YOUNG, Theresa B. University of Wisconsin (Madison) 1 R23 CA 38000-01	Epidemiologic Study of Colon Cancer in Wisconsin
157.	ZELEN, Marvin Dana-Farber Cancer Institute 2 R01 CA 23415-08	Statistical Models of Biomedical Phenomena
158.	ZIMMERMAN, Stuart O. University of Texas System Cancer Ctr. 2 R01 CA 11430-19	Biomathematics and Computing in a Cancer Institute

CONTRACTS ACTIVE DURING FY 85

	Investigator/Institution/Contract	Title
159.	AZIZ, Faye Social Security Administration Y01 CP 30501	Test of the Continuous Work Sample of SSA as a Probe for Cancer in the Workplace
160.	DETELS, Roger University of California (Los Angeles) N01 AI 32511	Natural History of AIDS in Homosexual Men
161.	FILIPOVICH, Alexandra University of Minnesota N01 CP 31011	Immune Deficiency and Cancer Registry
162.	POLK, B. Frank Johns Hopkins University N01 AI 32520	Natural History of AIDS in Homosexual Men
163.	RINALDO, Charles R., Jr. University of Pittsburgh N01 AI 32513	Natural History of AIDS in Homosexual Men

164. SCHEUREN, Frederick
Internal Revenue Service
Y01 CP 50500

Test of the Usefulness of IRS Occupation Codes in Determining Mortality Differentials through the CWHS