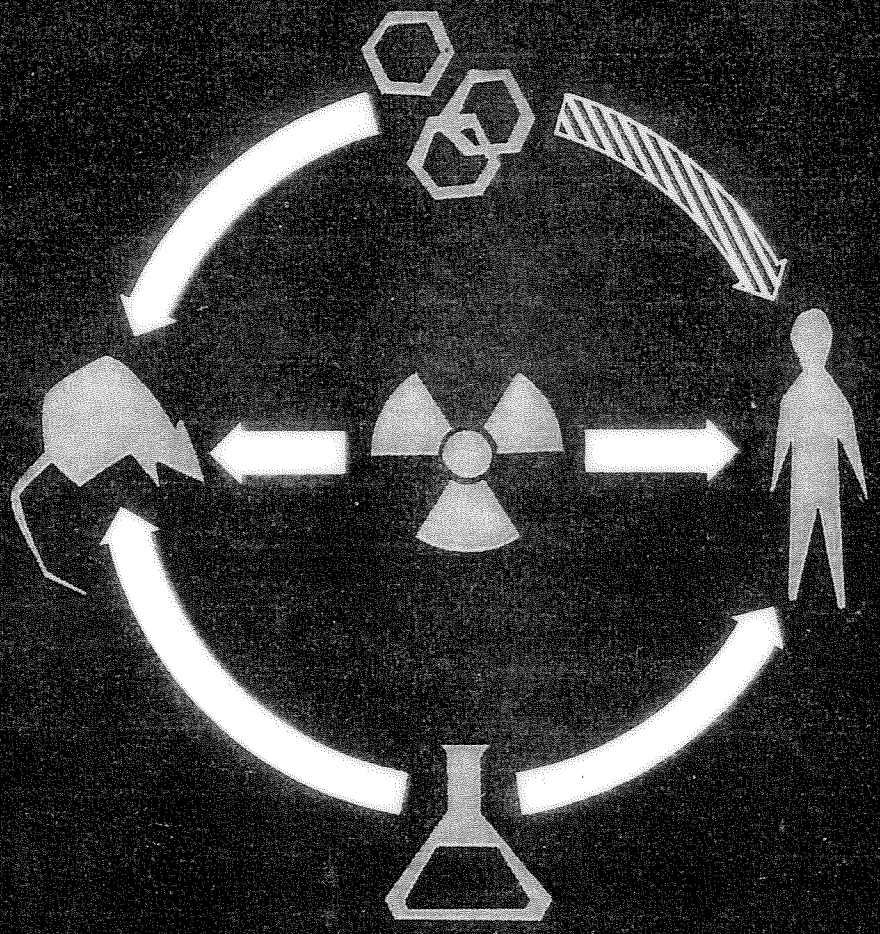
special virus - cancer program

August 1972



Division of Cancer Cause and Prevention
National Cancer Institute

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Institutes of Health

SPECIAL VIRUS CANCER PROGRAM

PROGRESS REPORT #9

Program Staff
Viral Oncology
Division of Cancer Cause and Prevention
National Cancer Institute*
July, 1972**

* National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda, Maryland.

** This report was prepared by senior staff of the Viral Oncology Area, Division of Cancer Cause and Prevention, NCI and submitted to NIH as the area's Annual Report in May, 1972. It was updated in July, 1972 for the Annual Joint Working Conference, SVCP, At the Hershey Medical Center, Hershey, Pa., October 29 - November 1, 1972.

PROGRESS REPORT

OFFICE OF THE ASSOCIATE SCIENTIFIC DIRECTOR FOR VIRAL ONCOLOGY (OASDVO)

July 1, 1971 - June 30, 1972

J. B. Moloney, Ph.D.

A. SPECIAL VIRUS CANCER PROGRAM (SVCP)

1. Introduction:

The Viral Oncology Area is responsible for planning and conducting the Institute's program of coordinated research on viruses as etiological agents of cancer. Scientists within this Area not only provide the broad operational management for intramural and collaborative research but also conduct investigations on oncogenic viruses and their interaction with host cells and apply this information to search for viruses which may be etiologically related to the initiation and continuation of human cancer.

Contract supported research is conducted within the Viral Oncology Program under the Special Virus Cancer Program (SVCP) whose primary objectives are: (1) to determine whether viruses comparable to those known to induce cancers of laboratory and domestic animals are causative agents of human cancers, and (2) to develop therapeutic and preventive measures for control of human cancers when such causative agents are found. A detailed history of events leading to the development of the SVCP may be found in previous Annual Reports of the NCI. In the eight-year history of the Special Virus Cancer Program, the National Cancer Institute has sponsored extensive research on the role of viruses as etiologic agents of cancers of man. The Program has succeeded in marshaling many of the nation's finest virologists, biochemists, immunologists, molecular biologists, epidemiologists, and physicians for this strongly goal-oriented effort. From the beginning, it was clear that an understanding of the suspected relationship between tumor viruses and human neoplasia would not only require an interaction among these groups of scientists but sound and constructive administrative support as well. Having provided the broad operational management and funds--the budget has risen from $10 million in 1964 to a projected $46 million for 1973--for an integrated contract program of international scope, Program leaders are confident that the objectives will be achieved.

The SVCP is changed, refined, and evaluated by the Science Management Team and its key advisors. The Program plan has undergone considerable revisions since its inception. This year the Research Logic Flow Chart was extensively revised and updated. It is based on the premise that a virus or viral genetic information persists in the diseased individual and is an indispensable element for the induction of certain kinds of human cancer. The Program plan is reviewed regularly by the Director, NCI; Scientific Director for Etiology, NCI; the National Cancer Advisory Board; The Scientific Directorate, NCI; and the Etiology Program Management Group, NCI.

2. Organization:

a. Viral Oncology Area. During the previous reporting period the Viral Oncology Area was reorganized into a structure that has permitted more effective use of scientists and facilities. This year one new Office was established within the Office of the Associate Scientific Director for Viral Oncology: the Office of Program Resources and Logistics. This change was effected with existing personnel, space, and funds.

This Office and its standing Advisory Committee have been given the task of implementing and coordinating contracts awarded to provide resources for both intramural and collaborative research and has assumed the responsibilities of the former Program Resources and Logistics Working Group, a Segment within the Special Virus Cancer Program. In the coming year, it is anticipated that a prime contract will be established to assist this Office in maintaining and substantially expanding the resources and integrated logistics support for the Area.

The specific functions of this Office are as follows: Plans and maintains a program to anticipate and meet the needs of the Viral Oncology Program (in house and collaborative) for resources and logistics support. Insures optimum use of government funds through careful selection of contractors, periodic review of contractors' performance, and management of collaborative research contracts. Documents all aspects of the resources and logistics program. Prepares an annual catalog which lists and describes the research resources available to the Program. Develops in collaboration with the Office of Program Analysis and Communication, a computerized central inventory for the sera, cell cultures, and human cell and tissue specimens acquired by the Program. Insures that research resources are always available for use by laboratory investigators.

Members of the Program Resources and Logistics Advisory Group are:

Dr. Jack Gruber, Chairman
Dr. Robert Bassin, NCI
Dr. James Duff, NCI
Dr. Robert Goldberg, NCI
Dr. Robert Holdenried, NCI
Dr. David Howell, NCI
Dr. Garrett V. Keefer, NCI
Dr. Timothy O'Connor, NCI
Dr. Wade Parks, NCI
Dr. Gary Pearson, NCI
Dr. Deward Waggoner, NCI

The Viral Oncology Area is organized as follows: The Office of the Associate Scientific Director for Viral Oncology includes four Offices: The Office of the Coordinator for Ultrastructural Studies with a Viral Studies Section; The Office of Biohazards and Environmental Control with two section, the Biohazards Research Section and Environmental Control Section; The Office of Program Analysis and Communications with one Information Unit; and The Office of Program Resources and Logistics.

The Viral Biology Branch includes six sections; Cell Biology Section, Electron Microscopy Section, Microbiology Section, Experimental Pathology Section, Human Tumor Studies Section, and Virus and Disease Modification Section.

The Viral Leukemia and Lymphoma Branch includes the Tumor Virus Section, Immunology Section, Viral Pathology Section, Genetics Section, and Molecular Biology Section.

The Viral Carcinogenesis Branch includes the Ecology and Epizoology Section, with the Field Studies Unit; the Solid Tumor-Virus Section; and the Viral Genetics Section, with the Serology Unit, and the Trailer Unit.

b. Special Virus Cancer Program

The Special Virus Cancer Program is currently composed of 5 working segments: Developmental Research Segment, Immuno-epidemiology Segment, Biohazards Control and Containment Segment, Solid Tumor Virus Segment, and Breast Cancer Virus Segment. Since the last reporting period, three working group segments were terminated: The Immunology Group, the Special Animal Leukemia Ecology Studies Segment, and the Program Resources and Logistics Segment; and a new Segment: The Immunology-epidemiology Segment, was established.

On September 28, 1971, the Immunology Group which had served on an ad hoc basis to review and manage contract proposals of an immunological nature for the entire Etiology Area was terminated. It was expected that other review bodies in this Area would then assume these responsibilities. On September 29, 1971, at the request of the Associate Scientific Director for Viral Oncology, the Scientific Director for Etiology approved the formation of a new segment known as the Immuno-epidemiology Segment. Contracts relating to the goals of the Special Virus Cancer Program were transferred to this Segment, whose mission is as follows: To develop and improve immunological techniques relevant to the determination of the etiology of neoplasia and its detection, prevention, and treatment; to apply the information gained from these studies to human cancer, with specific reference to the detection, prevention, and treatment of human tumors, especially those of possible viral etiology.

Because the mission of the Special Animal Leukemia Ecology Studies Segment was successfully accomplished, this working group was terminated on October 1, 1971. In existence since the inception of the Program, this working group was responsible for conducting research on the etiology of animal tumors and their possible interrelationships to man. Over 100 viruses known to cause tumors in vertebrate species were discovered and characterized; evidence for a causal relationship between animal tumor viruses and human cancer was entirely negative. Contracts within this segment were distributed, therefore, to other working groups to provide for better coordination and integration of studies on model systems with research on the viral etiology of human cancer.

On March 1, 1972, the responsibilities of the Program Resources and Logistics Segment were transferred to the Office of Program Resources and Logistics in the Associate Scientific Director's office. The reasons for this change are given in Part B, item 1 of this report.

With the advent of many new immunological and biochemical methods for the detection of viral antigens and/or viral activity within cells, it is anticipated that in the next year a new segment, the Tumor Virus Detection Segment, will be established.

Program Management

Segment Chairmen. The program segment chairman is responsible for planning the projects in each working group. As a senior scientist, he must review, analyze and integrate studies which fulfill the objectives of his working group and the total Program. The chairman is aided in this task by a vice-chairman, executive secretary, and working group members composed of intramural and extramural scientists.

Project Officers. The project officer is the direct extension of the program segment chairman. To assure progress in accomplishing the goals set forth in the workscope of a project, he is called upon to advise the principal investigator on scientific matters and inform him of segment and program decisions.

Executive Secretaries. The executive secretary assists the segment chairman and project officers in managerial duties of contract operation. He is responsible for optimal review and documentation of each project within the working group.

Contract Specialists. The contract specialist is now responsible for negotiating research contracts. He provides valuable advice on fiscal and legal matters to the project officers, executive secretaries, segment chairmen and Associate Scientific Director. Some specialists are well conversant with the scientific aspects of the Program.

Working Groups. The program segment working group is the basic review unit for the Program. Composed of both intramural and extramural scientists and chaired by a senior NCI scientist, the group reviews individual contracts or proposals for scientific excellence and technical competence within a given funding level. Its recommendations provide the Segment Chairman, Associate Scientific Director, and the Scientific Director with a basis for program decisions.

Contract Review.

The projects within the total Program are reviewed, both formally and informally, at three levels:

(1) Each contract is reviewed for relevance, priority, and need to total Program at the Program Segment Chairmen's meeting.

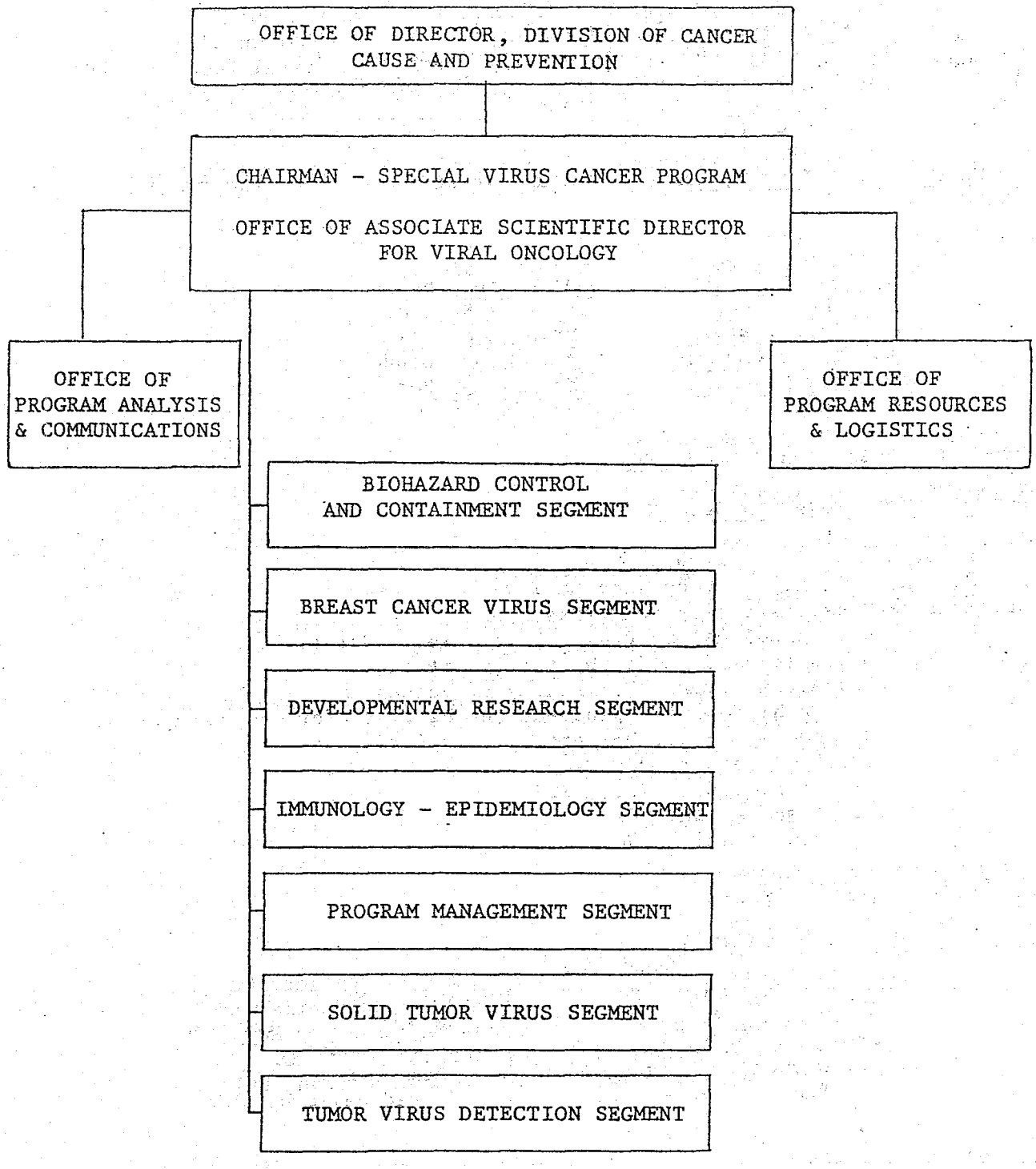
(2) Each contract is reviewed for scientific excellence and technical competence at the Program Segment Working Group meeting.

(3) Each contract is reviewed for performance by the Project Officer.

As an aid to the review processes, key staff members receive progress reports on all contracts on a triannual basis. Collection and distribution of these reports is the responsibility of the Office of Program Analysis and Communications. A single comprehensive report is prepared annually by the Associate Scientific Director.

ORGANIZATIONAL CHART

SPECIAL VIRUS CANCER PROGRAM



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Dr. L. R. Sibal, Assistant for Program Coordination, Viral Oncology, NCI
Dr. D. J. Rubin, Assistant for Collaborative Research, Viral Oncology, NCI
Dr. H. J. Hearn, Scientific Coordinator for Viral Oncology, Frederick Cancer Research Center

Administrative Officer, Assistant Administrative Officers and Contract Specialists

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Mr. Robert Seely	Mr. Sam Kuschner
Mrs. Anna Beattie	Mr. J. Thomas Lewin
Mr. Wm. L. Caulfield	Mr. Thomas Louden
Mr. Charles Fafard	Mr. Thomas Porter
Mr. Maurice Fortin	Mr. Fred Shaw

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Dr. Michael Chirigos, Acting Vice Chairman
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Dr. Samuel Dales, Public Health Res. Institute, N.Y.C.
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Dr. Arthur Brown, University of Tennessee
Dr. Mathilde Krim, Sloan-Kettering Inst. for Cancer Research
Dr. Malcolm Pike, University of Oxford
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Dr. Bernice Eddy, DBS, NIH
Dr. Alan Rabson, NCI
Dr. Robert Gallo, NCI

Program Management Segment

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Dr. Edmond Klein, Roswell Park Memorial Institute
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Dr. Guy Newell, Tulane University
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Dr. Carrie Whitmire, Microbiological Associates

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Dr. Lauren Wolfe, Presbyterian St. Luke's Hospital

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Dr. Paul Zamecnik, Massachusetts General Hospital

3. Scientific Activities

The summary reports of the Office of the Associate Scientific Director for Viral Oncology and of the Offices and Branches within this Office are presented in the following sections. Highlights of these reports demonstrate that the Viral Oncology Area through its intramural and collaborative research programs has already provided a broad base of information on the characteristics of tumor viruses and is applying this knowledge to the isolation and identification of human tumor agents.

SUMMARY REPORT

Introduction. A considerable number of viruses are known which either directly or indirectly cause tumors in different vertebrate species. Many of these replicate in cultured human cells, and some cause cellular transformation. Since the RNA viruses are responsible for many naturally occurring tumors in animals, this group is most likely to be the cause of some human neoplasms. Although no virus has yet been proven to induce human cancer, it would be unreasonable to consider man to be the exception. Certain DNA viruses may also be involved in oncogenesis. Herpesviruses, in particular, are known to induce lymphoproliferative diseases in several animal species. The close association of these viruses to human malignancies suggests that they may play a causal role or act as necessary co-factors in tumor formation.

RNA VIRUSES

Characteristics. RNA tumor viruses have a number of similar biological and biochemical characteristics. They are widely distributed in vertebrate animals: the chicken, snake, mouse, rat, hamster, cat, cow, and non-human primates. Vertical rather than horizontal transmission is probably the natural means by which they are perpetuated and may account for their common occurrence in certain animals. Infections are not necessarily associated with virion release or the development of neoplasms. Apparently the information for making a Type C virus can be incorporated into the chromosomes of the host and is passed on as a heritable factor. In such covert infections, there is only partial expression of the full antigenic complement of the viral gene and the infected animal often remains tolerant to these antigens. While activation of tumor virus expression or infectious virus may occur spontaneously as a result of aging or following exposure to carcinogens in the environment, some viruses are defective and require co-infection with another virus for maturation. The host genes also have been shown to have a profound effect on the virogenic and tumorigenic expression of RNA virus in normal tissue. Immunogenetic studies on recombinant inbred lines of mice have identified the genes responsible for host response to both exogenous and endogenous virus expression, replication, and tumorigenesis and for the host range of tumor viruses. The gene responsible for gs-antigen expression (gs+) of a murine leukemia virus is transmitted as a simple Mendelian dominant; another has been identified as a

determinant of virus replication and segregates independently from the gs-determinant gene.

Each Type C virus, regardless of origin, possesses a major internal protein of approximately 30,000 molecular weight. This protein (gs-1) has a species-specific isoelectric point and carries determinant groups which permit delineation of the species of origin. The specific reactivity appears to be an invariable characteristic of the virus regardless of what cell type is used to propagate the virus. The mammalian viruses also share a determinant, perhaps on this same protein, which is inter-species specific (gs-3). A third antigen (gs-2) has been isolated recently but it is not yet well-characterized. Two group specific antigens of the Type B particles producing murine mammary tumors (s_1 and s_2) have recently been isolated and characterized. These are antigenically dissimilar to corresponding antigens of the Type C viruses. All of these viruses contain 60-70S RNA and an enzyme, RNA-dependent polymerase which has the property of assembling DNA copies of viral RNA. The enzymes from the different mammalian Type C viruses are antigenically related but not identical; those of the mouse mammary tumor virus and avian leukosis viruses are antigenically distinct. With the possible exception of certain foamy viruses and viruses producing "slow diseases", the presence of this enzyme may be unique to the RNA tumor virus group.

Information on the RNA tumor viruses together with data acquired by extensive studies on laboratory and feral mice has led to a theory of RNA viruses as determinants of cancer. It proposes that these viruses exert their oncogenic action directly on information already present in all cells, the oncogene. The information carried within the virus particle (virogene) is transmitted to succeeding generations of cells in covert form in a normal pattern of inheritance; expression is controlled by host regulator genes and repressors within the normal adult cell. Derepression, which may occur with advancing age, upon exposure to environmental carcinogens, or following infection with certain DNA viruses, results in tumor development and possibly virus release. The idea is simple: if all cells vertically inherit oncogenes, transformation to malignancy depends on whether its oncogenes are switched on; similarly, the release of an RNA tumor virus depends on whether its virogenes are also expressed.

The one major criticism of this theory--its difficulty to test--has not prevented collecting evidence in favor of it. For example, it was recently shown that apparently normal, gs+ chick cells spontaneously release a Type C virus which can be classified as an avian leukosis virus; even gs- cells, following treatment with mutagens (BrdU), and ionizing radiation, start to release a similar virus. Virus-free clones of AKR mouse embryo cells on exposure to mutagens, or following transformation with DNA viruses produce a virus identical to one that causes leukemia of AKR mice. Understanding of the mechanisms whereby the oncogene is repressed or derepressed offers excellent possibilities for preventing or modifying virus-induced cancers.

Relationship to human cancer. The nature of the virus-host relationship recognized in the RNA tumor viruses demonstrates the difficulty in establishing definitive associations of viruses to the oncogenic process in man. Several lines of investigation have been followed: human populations were studied to determine whether exposure to known viruses might be a factor in the incidence of cancer; efforts were increased to detect and recover viruses from tissues of cancer patients; and more recently, investigations were initiated to determine the molecular pathways for virus replication, integration into the host genome, and neoplastic transformation.

Studies were conducted to determine whether possession of household pets influenced the familial incidence of cancer. The ease with which the feline leukemia and sarcoma viruses infect human cells in culture suggested a potential hazard for man. Virus has been detected in the saliva and tissues of leukemic cats, and is present in some apparently normal animals. Accordingly, surveys were initiated to determine whether a significant difference existed in the incidence of cancer among families owning cats and dogs, and those without pets, but none could be demonstrated. Although no antigens reactive with an antiserum to feline leukemia virus were found in lymphomatous and non-lymphomatous tumors of other species including man, further confirmation negating natural infection of man may be required.

The recent demonstrations of three RNA viruses in different primate species may eventually be the best models for the study of the viral etiology of human cancers. Two Type C viruses isolated from a sarcoma of a Wooley monkey and from a lymphoma of a Gibbon ape can be propagated in cell culture in amounts sufficient to provide important immunodiagnostic reagents. They have a common group antigen and a polymerase with properties characteristic of tumor viruses, but distinguishable from Type C viruses of lower animals. Similarly, a spontaneous mammary carcinoma which arose in a Rhesus monkey was found to contain appreciable amounts of a virus resembling the Type B particle causing murine mammary tumors. The virus not only replicates in monkey embryo cells but is infectious for cultured chimpanzee and human cells. The particles contain a polymerase similar to that found in RNA tumor viruses. Tests for oncogenicity in the Rhesus monkey are not yet well enough along to expect results. The finding of Type C and Type B viruses in tumors from old and new world primates greatly increases the likelihood that related viruses will also be found in human tumors.

Considerable effort was expended in the search for RNA viruses which might be oncogenic for man. Type C viruses resembling those of murine leukemia were discovered in the lymph nodes and blood plasma of leukemic patients. Since identification of free particulates as viruses is somewhat subjective, budding mature forms in tumor cells were sought with limited success. Although free virus or virus-like particles appeared occasionally in cell cultures, regular release of sufficient numbers of particles for study was not achieved. A culture originating from a liposarcoma apparently did release Type C particles, but virus production was not

sustained. For the past several years, sufficient numbers of observations reporting the finding of particles similar to the Type C and Type B in human malignancies have been made to conclude that viruses of these types may also infect man. The occasional presence of mature virus particles in human tumors, however, may be the exception rather than the rule.

With the development of new immunological and biochemical methods to detect Type C and Type B viruses or virus expression (polymerase activity assay, radioimmunoprecipitation inhibition assay, etc.), the finding that thymidine analogs (BrdU) are efficient virus inducers, and recent advances in molecular biology, the possibility of finding virus or virus expression in human tumors has increased by several orders of magnitude. Within the last year alone, four candidate RNA tumor viruses have been isolated and are being propagated in cell culture: ESP-1, RD-114, "Stewart virus", and a virus from the milk specimen of a woman with breast cancer. At the present time only two of these viruses are well enough characterized to describe further. ESP-1 was first isolated from cultures of cells in the pleural effusion from an American-type Burkitt's lymphoma patient. Investigations on the true origin of this virus are still under way and should be resolved soon. RD-114 virus was isolated from culture of a brain tumor of a fetal cat inoculated with human rhabdomyosarcoma cells. Intensive studies have already shown that the virus lacks the gs-1 antigen and shares the gs-3 antigen of known mammalian Type C viruses; the polymerase is related to the enzymes of the recently isolated primate Type C viruses. More data are obviously needed to confirm its human origin.

The finding that RNA tumor viruses of chickens or mice contain an enzyme with the property of assembling deoxyribonucleotides into specific DNA in the presence of an instructing RNA opened a new approach to the study of virus-induced cancer. Biochemists had known only enzymes capable of copying the genetic information contained in the nucleotide sequences of DNA into DNA or RNA copies. Soon it was demonstrated that reverse transcriptase was present in all the RNA-containing tumor viruses derived from many different animal species. The availability of substantial quantities of AMV permitted development of procedures for purification of this enzyme. It has been purified several hundredfold and shown to consist of a complex of two proteins having molecular weights of 110,000 and 69,000. The enzyme associated with other cancer viruses has been purified and shown to have generally similar properties. Many features of how the enzyme operates at the molecular level have now been elucidated.

Three findings from these studies appear to merit special mention in view of their practical consequences. First, a simple procedure for simultaneously detecting both the unique high molecular weight RNA and the enzyme reverse transcriptase of cancer viruses has been developed. This simple and rapid biochemical test provides a method for detecting cancer viruses and powerfully augments the much less sensitive and slower electron microscope examinations previously employed. The test has already shown utility in investigations of the role of viruses in human cancers.

Second, other studies indicate that the reverse transcriptase enzymes isolated from different cancer viruses have distinct immunological characteristics which are useful for typing the virus as to function (e.g. breast cancer, leukemia virus) and species of origin. This finding, combined with earlier data on other type-specific and interspecies group-specific antigens of cancer viruses, provides a range of serological characteristics for classification of suspected human cancer-virus candidates. Third, it has been shown that the reverse transcriptase enzyme from AMV can be used to prepare DNA copies of the RNA of other cancer viruses: DNA complementary to the RNA of mouse leukemia virus and mouse mammary tumor virus has been prepared. The last finding derives its importance from the availability of specific hybridization procedures.

Within the past year applications of these three new procedures arising from studies on animal viruses have developed significant new data relating to human cancer problem. About a year ago evidence from electron microscopic studies was presented that human milk specimens, particularly those obtained from women whose family histories would indicate increased risk to breast cancer, contained particles similar to the known mouse mammary tumor virus. It was then shown that the presence of such particles coincided with the presence of detectable reverse transcriptase activity in human milk. The procedure was also used to demonstrate the presence of appropriate RNA and reverse transcriptase in purified viral particles isolated from human milk specimens, and to monitor and establish conditions for the successful infection and propagation of the suspected human breast cancer virus in human cell cultures. Preliminary results from these studies seem promising.

In a study of mouse mammary tumors induced by MTV, DNA complementary to MTV RNA, made from MTV-RNA with the aid of AMV reverse transcriptase, specifically hybridized to the RNA obtained from mouse breast tumors. The RNA used in these experiments was isolated from the microsomal fraction of the tumor cells and thus presumably contained messenger RNA in the process of being translated into protein. The DNA failed to hybridize to the RNA isolated from the microsomal fraction of normal mouse breast tissue. The DNA also failed to hybridize to the RNA isolated from mouse leukemia virus but did, as expected, hybridize to the RNA obtained from MTV.

These studies were extended to examine human breast tumors. Nineteen of 29 specimens of human breast cancers yielded microsomal fractions which hybridized with DNA complementary to mouse MTV RNA. These microsomal RNA fractions failed to hybridize to DNA complementary to mouse leukemia virus RNA. Normal breast tissue specimens or breast tissue from various benign lesions gave microsomal RNA fractions which did not hybridize with DNA complementary to MTV.

This approach was then extended to the study of human leukemias and sarcomas. It was observed that the white blood cells of 24 out of 27 leukemic patients examined yielded polysomal RNA which hybridized to DNA

complementary to the mouse leukemia virus, but not to the DNA prepared from unrelated viruses causing mammary tumor in mice or myeloblastosis in chickens. No control human white blood cells or other adult or fetal tissues showed significant levels of the leukemia-specific RNA. Eighteen of 25 specimens of microsomal RNA from human sarcomas hybridized to the DNA complementary to mouse leukemia virus RNA, but not to the DNA complementary to mouse MTV.

The above findings suggest that human breast tumors contain functional genes which are related to the genes contained in the virus known to induce mammary tumors in mice. Human leukemias and sarcomas also appear to contain different functional genes related to the viruses known to induce leukemias and sarcomas in mice and other animals. In each case, the viral-related genes in the human tumors are functional in that some proteins are presumably being synthesized. At this time, it is not known if all the proteins required for production of complete viruses are being synthesized or whether synthesis is restricted to include certain proteins which are involved in the cancer transformation of the cell. It can, however, be anticipated that efforts will be expanded in the coming year to determine the possible implication of both the virus particles obtained from human milk and the RD-114 virus in human cancers.

DNA VIRUSES

Characteristics. There is also evidence linking the etiology of several human tumors to DNA viruses, especially those of the herpesvirus group. As with RNA tumor viruses, diseases of animals have provided useful model systems. Herpesviruses recovered from wild rabbits, chickens, and higher primates induce lymphoproliferative neoplasias in their respective hosts and the association of a virus from frogs with kidney carcinoma is well known.

In general, herpesviruses can show either productive or non-productive growth cycles. Cell death invariably accompanies the production of virus particles and the course of this production is similar for all members of this group. In common with other oncogenic DNA viruses of animals, certain herpesviruses stimulate cellular DNA synthesis and transform cells with finite growth capability into cultures with infinite growth potential. But, herpesviruses like the RNA tumor viruses also establish persistent covert infections. There is no definite evidence that they are vertically transmitted in vivo in a manner analagous to RNA tumor viruses, but transmission of the genome present in non-productive, cultured cells to progeny can occur. Activation of virus production also occurs in "virus-free" cells after exposure to mutagens (BrdU) and irradiation, supporting the idea that this group of viruses, although normally cytocidal, has oncogenic potential.

The question has been raised as to whether such herpesviruses produce their effects by expression of genes different from those involving cancers induced by RNA containing viruses, or whether such herpesviruses may indeed not be intrinsically cancerous but produce tumors through an

aberrant response of the infected host. Such tumors are now being examined for the expression of viral-related genes.

Relationship to human cancer. Over the past several years, viruses of the herpes type have been associated with certain human cancers: Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, infectious mononucleosis, and cervical carcinoma.

A herpesvirus, the Epstein-Barr virus (EBV), may be a contributing factor in the genesis of Burkitt's lymphoma. The mode of infection and site of production of EBV in this disease is unknown. Immunoglobulin production shows that Burkitt's lymphoma cells are monoclonal in origin, indicating that the tumor may not be of multifocal origin. A virus cause of this tumor is suspected because it occurs in high incidence in regions of Africa favorable for insect-vectored disease. Moreover, cases in certain areas cluster in time and space. EBV has been regularly isolated from tumor tissue, suggesting this virus may be the cause of the disease. Most patients with tumor have high titers of antibody to the viral antigens. However, a large proportion of normal people of all ages have antibodies to the virus, though usually in low titer. Further studies have shown that primary EBV infection of young adults caused some forms of infectious mononucleosis. Therefore, EBV may simply be a passenger within lymphoma tissue, isolated with regularity because it has a predilection of the lymphocyte and is widely distributed in humans. Existing information does not permit resolution of the question, but several aspects of the association of EBV infection with this tumor support a more than passive role. The high titer of antibodies in patients with Burkitt's tumor is not characteristic of other lymphoproliferative conditions. Even though 95 percent of normal African children may have antibodies, one would expect that a few tumor cases would be sero-negative were virus infection not an integral feature of the disease.

The lymphoma patient possesses a greater spectrum of antibodies to the several antigenic components in virus-infected cells than does the normal individual. The presence of certain antibodies appears to be related to the condition of the patient with respect to tumor. Antibodies to the membrane antigens in EBV infected cells as well as precipitating antibodies fell to negligible titer when a treated patient was followed during tumor regression and rose when tumor recurred months later. The recently isolated EBV-induced early antigens (EA) were found to be more disease associated than the viral capsid antigen. Two antigenic components were differentiated in the EA complex by indirect immunofluorescence tests: the D or diffuse staining complex and the R or restricted complex. For prognostic purposes, the presence or absence of antibodies to the early antigens appears to have important implications. The serums of a majority of patients with Burkitt's lymphoma contain antibody to the R antigen; the absence of antibodies is a favorable sign.

The response of lymphocytes to infection also suggests that EBV may have some attributes of the oncogenic RNA viruses. Lymphocytes from EBV negative donors fail to grow in continuous culture unless they are exposed to

infectious EBV. This apparent cellular transformation is attended by chromosomal aberrations, a feature associated with herpetic infections. Not all long-term lymphoblastoid cell cultures release EBV and may not contain antigens demonstrable by immunofluorescence tests. Nevertheless, the presence of EBV antigens has been detected by serologic tests and by homology of cellular DNA and mRNA with viral DNA. Such evidence of covert infection has been extended to biopsies of tumor tissues. Primary tumor rarely shows any cells positive for EBV by immunofluorescence, but all tumors examined have contained DNA homologous to viral DNA. Clones of EBV positive cells release virus as did the parent culture. Evidently, the virus genome persists in cells, frequently with minimal antigenic expression, and is transmitted to progeny during cell division. Thus, biologically this virus resembles the RNA tumor viruses.

While there is good reason to believe that EBV is involved in the oncogenic process, its role could be that of an accessory factor. High antibody titers to virus antigens are consistently found in patients with diseases other than Burkitt's tumor. These include nasopharyngeal carcinoma, the sarcomatous form of Hodgkin's disease, and some cases of sarcoidosis. Although examples of a causal relationship between one virus and different manifestations of malignant disease are known in avian and mammalian systems, the situation with regard to EBV is one of apparent rather than demonstrable direct association.

High EBV antibody titers, at least in some disease states, may be secondary to the disease process. In fact, not every individual bearing Burkitt's tumor has a high anti-EBV serum titer. Tumors of the Burkitt type do occur in temperate regions. Therefore, some combination of environmental factors unique to Africa does not appear to be an essential feature in the etiology of this disease.

If we assume that infection by EBV primes the cell for neoplastic change, it is possible to conceive that one or more combinations of environmental and host factors could interact to promote oncogenesis. Thus, the association of EBV infection with more than one disease becomes more plausible. Should EBV prove to be a necessary co-factor in any or all diseases with which it appears to be associated, control of infection by this virus would be of paramount importance. The prospective seroepidemiological study on a sizeable population of children in an area where tumor occurs with relative frequency should do much to clarify issues. The availability of an animal host susceptible to infection by EBV would also aid in the study of this virus.

Genital strains of Herpesvirus hominus Type 2 might be a contributing factor in carcinoma of the uterine cervix. Seroepidemiological studies conducted in several cities in the United States showed that significantly more women with invasive carcinoma have antibodies to this virus than do women without this tumor. The incidence of this neoplasm is related to sexual experience. The cancer is rare in nuns and most prevalent in promiscuous women, where the exposure to infection by the virus is expected. When these studies were extended to selected groups of women

in other countries, the results were not as conclusive. The question arises whether the methods applied are not sufficiently discriminating to permit detection of antibodies to certain genital strains in the presence of antibodies to oral strains of the virus, or whether the tumor-virus relationship is simply fortuitous. According to some investigators, there remains a significant difference between the rate of herpesvirus Type 2 antibodies in cervical patients compared to controls and further epidemiological studies will continue in this area.

PROGRESS HIGHLIGHTS
(Not considered in Scientific Activities Narrative)

RNA Viruses

Previous studies showed that rat and hamster cells infected with RNA tumor viruses provided extremely rapid, sensitive, and reproducible transformation assay systems for carcinogenic chemicals. After testing large numbers of non-carcinogenic analogs together with their related carcinogens in a standardized rat Rauscher leukemia virus-infected cell system, the positive and negative results agreed remarkably well with the known in vivo carcinogenic activity of these compounds.

A rapid, sensitive assay has been developed to detect RNA-DNA and DNA-DNA hybrids by the use of nucleases (Aspergillus sp., mung bean) that will degrade only single-stranded nucleic acids, leaving hybrid structures intact. This assay could eventually replace the more costly and time-consuming hydroxyapatite chromatography or $CsSO_4$ equilibrium centrifugation methods.

A genetically stable change in host range and the development of new viral surface antigens occurs in an animal RNA tumor virus after prolonged passage in human cells. The most exciting interpretation of these findings is that recombination has occurred with a Type C human virus, which itself may exist in an integrated form within the host cell genome. The new viral surface antigens would then reflect the genetic information of the latent virus and could be useful markers to search for evidence of a viral etiology of human cancer. These observations also emphasize that caution must be exercised in evaluating new viruses isolated from human cancers since they may in fact be animal viruses with human "outer coats."

Molecular hybridization experiments employing the DNA products of avian and murine tumor viruses and DNA of normal and tumor cells show that DNA copies of the virus produced by the reverse transcriptase sequences are present in normal as well as tumor cells, regardless of whether they have infectious virus. Normal cells, therefore, contain part or all of the sequences necessary to make RNA viruses.

Structural studies on the 70S RNA of avian oncogenic viruses indicate that the 70S molecule consists of 35S subunits. These subunits are linked by hydrogen bonds to form the 70S complex. Two size classes of subunits can be resolved by electrophoresis in polyacrylamide gels. The larger class has been found exclusively in sarcoma viruses whereas the smaller class

occurs in sarcoma and leukosis viruses. This evidence suggests that RNA subunits contain genetic information which is required for transformation of fibroblasts; the subunits of tumor virus RNA can therefore be considered as functionally specialized.

Studies on the RNA-dependent DNA polymerase suggest that this enzyme functions as a repair enzyme to produce a complementary copy of a single strand of RNA by building from the terminal end of a primer strand linked to the template strand. This finding suggests that this enzyme, present in virions, is not directly involved in the replication of the RNA of tumor viruses.

Antigens of the Mason-Pfizer monkey virus (M-PMV), previously isolated from a breast cancer of a Rhesus monkey and shown to contain both 70S RNA and reverse transcriptase, have been found to be present in two of five normal Rhesus monkey embryos. This finding suggests that M-PMV may be indigenous and vertically transmitted in this species.

A method was developed permitting the detection of two markers of RNA tumor viruses, the 60-70S RNA and reverse transcriptase activity, within crude specimens containing relatively small numbers of particles. It is now possible to characterize particles detected in specimens from human cancer patients in terms of their content of high molecular weight RNA and of RNA dependent-DNA polymerase.

Highly purified (electrofocused) species-specific gs antigens and antisera have been prepared for the RNA tumor viruses of the following species: mouse, rat, cat, hamster, human? (RD114), viper and chicken; each one is species-specific in gel diffusion, radioimmune precipitation inhibition, and complement-fixation.

A Type C virus, continuously released by the R-35 cell line established from a spontaneous mammary carcinoma of the rat, infects and transforms cells. When implanted into rats, these cells produced tumors of possible mammary gland origin.

DNA Viruses

Herpesvirus saimiri (HVS), a virus inducing a lymphoproliferative disease in squirrel monkeys, can now be studied to determine its natural mode of transmission and pathogenesis in different primate species. The virus is widely distributed in squirrel monkeys and can be isolated readily from blood samples. These observations suggest that the agent is highly infectious and transmitted horizontally within this susceptible monkey population. Recently owl monkeys inoculated with HVS have consistently developed malignant lymphoma and lymphocytic leukemia. Usually more than one injection of virus was needed to induce disease. No Old World monkeys have developed tumors over a period of two years. This virus presents a primate model to study oncogenicity by herpesvirus infection in a species closely related to man.

"Oncogenic" DNA virus transformed mouse cells were transplanted into

newborn Swiss mice. The resulting tumors were strongly positive for gs antigen but negative for infectious virus. Since the DNA virus does not cause tumors in the natural host, these findings favor the hypothesis that neoplastic changes produced in heterologous cells and animals by these viruses are due to derepression (or activation) of the RNA virus genome.

Under germ-free conditions, chickens which appear to be free of leukosis viruses respond differently from conventional chickens which develop typical symptoms of Marek's disease when infected with Marek's disease virus. The fact that germ-free birds succumb to infection with lesions of the central nervous system suggests that Marek's disease may represent an interaction between the host, Marek's disease virus, and a leukosis virus.

Recent preliminary findings stemming from the discovery of unusual clusters in the Albany, N. Y. area lend credence to the possibility that Hodgkin's disease may be infectious. There is no evidence, however, that this disease as it occurs in man is of a contagious nature. Virologic studies have concentrated on the possible role of EBV in Hodgkin's disease. Patients with this disease showed high antibody titers to EBV, similar to those found in patients with Burkitt's lymphoma. The results must be interpreted with caution since elevated antibody titers may be the result of the disease rather than a reflection of its etiology.

Treatment and Control

A new category of "unblocking or deblocking" antibodies that abrogates blocking antibodies was found in the sera of patients whose cancers were surgically removed or in remission.

An increase in the immunogenicity of weak tumor (SV40, MC transformed) cell surface antigens was obtained by incorporating influenza virus antigens into the cell surface membranes. Following formalin treatment to inactivate the influenza virus, vaccination of animals with homogenates of these cells gave significant protection to animals against challenge with viable cells of that tumor.

Streptonigrin in nanogram doses is highly effective in inhibiting replication of murine leukemia and sarcoma viruses in vitro. A marked decrease in titer of MLV (Rauscher) recoverable from infected mice as well as an increase in survival time of these mice was observed in those groups treated with this antibiotic.

Sera and lymphocytes from several thousand cancer patients were assayed in cytotoxicity tests for reactivity to more than 60 different cultured tumor cells having 25 separate HL-A antigens. The studies suggest that a genetically susceptible population of individuals exists with a higher risk of developing Hodgkin's disease, cervical cancer, and lung cancer.

Although Rifampicin and the related antibiotics are inactive, certain 3-substituted Rifamycin SV derivates are potent inhibitors of cancer

virus reverse transcriptase. Most of the active derivatives also inhibit other DNA and RNA polymerases normally present in the mammalian cell and thus are toxic, but a few do show a degree of selectivity against particular enzymes. A few compounds appear to show selective toxicity for leukemic lymphocytes as compared to lymphocytes from normal human donors. The possibility of molecular control of cancer through tailoring of compounds aimed at either killing cancer cells or reverting them to normal behavior through blockade of specific gene functions associated with cancer appears promising.

AKR mice have been considered immunologically tolerant to GMuLV, since they are G antigen positive during their entire life span. Recently, kidney-eluates of untreated AKR mice were found to contain at least two different antibodies to intraviral G antigen(s) and GCSA, although no free antibodies are detected in the body fluids. These findings indicate that there is no absolute immunological tolerance in the Gross leukemia system.

Immunization of AKR mice with neuraminidase treated thymocytes was effective in the prevention and control of leukemia in this species. This finding indicates that tolerance in AKR mice may not be complete and that treatment regimens of chemotherapy and immunotherapy may be effective.

MEETING REPORTS

The Viral Oncology Area through the Special Virus Cancer Program has endeavored to encourage cooperative research in this field by supporting meetings of major interest to viral oncologists throughout the world. The Program not only provides substantial funds to support the travel and expenses of scientists within the collaborative program but other U.S. scientists as well. In the last fiscal year alone the SVCP co-sponsored the following meetings: The Second International Congress for Virology, Budapest, July, 1971; Vth International Symposium on Comparative Leukemia Research, Padova/Venice, September, 1971; Symposium on Viral Neoplasia, University of Tennesse, Knoxville, May, 1972; 7th International Symposium on Breast Cancer in Animals and Man, Grenoble, June, 1972. Monographs of the papers presented at three of these meetings will be published.

Scientists representing laboratories throughout the world participated in the Sixth Annual Joint Working Conference of the Special Virus Cancer Program held at the Hershey Medical Center, Hershey, Pennsylvania, on October 24-27, 1971. The Joint Working Conference is held annually to provide for both formal scientific presentations as well as informal discussion by senior scientists representing the contract program and invited guests engaged in research on the viral etiology of cancer. The highlight of the first evening was the presentation of the first annual Special Virus Cancer Program (SVCP) Award to Dr. Joseph W. Beard, Duke University, "In Recognition of (his) outstanding contribution to Cancer Virus Research". This year five scientific sessions were held to present the most recent findings on: I. Detection of Virus or Virus Expression; II. Epidemiologic Studies; III. Host and Virus Genetic Factors; IV. Human Tumor Immunology; and V. Molecular Virology Studies. A summary of these sessions was

published in the J.N.C.I. (May 1972).

In addition to its Annual Working Conference, the SVCP also organizes and supports several conferences which emphasize new findings in tumor virology. The Solid Tumor Virus and Developmental Research Segments conduct several one-day scientific symposia known respectively as the PACTVIGR (Pacific Coast Tumor Virus Group) and the ACTVIGR (Atlantic Coast Tumor Virus Group). Reports of these meetings are summarized below. Two additional workshops--one on Cell-Mediated Immunity (Immunology-Epidemiology Segment) and another on Biohazards in Tumor Virus Research (Biohazards Control & Containment Segment) are also described.

Pacific Coast Tumor Virus Group (PACTVIGR)

This group was established in September, 1969 by Dr. Robert J. Huebner, Chief of the Viral Carcinogenesis Branch (VCB), NCI; and Chairman of the Solid Tumor Virus Segment, to promote maximum communication and collaboration among the Segment's contract scientists on the West Coast where many of its major contractors are located. PACTVIGR was designed to provide a working forum to compensate for the relative isolation of individual contractors from each other.

Dr. Leonard Hayflick, Stanford University, was appointed Chairman of PACTVIGR and has served in this capacity since its inception. Together with the VCB staff, he has organized the format and agenda, which emphasize new findings in the Segment programs on the West Coast and elsewhere. SVCP program leaders on the East Coast and some Eastern contract scientists are usually invited to participate as indicated by the theme of a specified PACTVIGR program. In general the meetings are attended by approximately 150 persons. Since the meetings are not considered "closed", the host laboratory and other contract laboratories in the vicinity of the meeting encourage their technical staffs to attend. In addition, interested outside scientists in the vicinity are invited.

During the first year (November, 1969 to September, 1970), six meetings were held at various research laboratories in the Northern and Southern California areas. These meetings were very successful in establishing active cooperative efforts between laboratories, thereby expediting research objectives within each contract operation and the program at large. During the past two years the meetings have been held on an average of once every three months.

Meetings 1, 2, and 4 followed the original plan: that is, individual laboratory progress reports from the participating laboratories, followed by an "in depth" report of the host laboratory, a tour of the host laboratory facility (for those interested), and invited presentations.

Meetings 3, 5-9 were devoted to selected subjects -- immunology, serology, molecular biology and genetics associated with the Type C viruses and viral genome expression in cancer and normal tissues of a number of species, including most recently simian and human.

The 10th meeting focused on naturally occurring primate and murine Type C

viruses, with emphasis on the putative human tumor virus, RD114, two recently isolated simian Type C viruses, and a variety of sensitive newly developed serological and immunological procedures for their study.

The most recent meeting (11th) was of particular interest. New (unpublished) epidemiological results were presented on the possible carcinogenic effects in offspring of women given diethylstilbesterol during pregnancy, possible environmental and infectious influences in the spread of Hodgkin's disease and a discussion of an epizootic of Rous-type sarcomas, hemangiomas, and nephromas among Marek's vaccinated chickens.

New findings of great potential significance were reports by Dr. Huebner and an East Coast contract group on prevention of chemically-induced tumors with a vaccine prepared from the murine Type C radiation-induced virus, and with interferon. These studies are now being followed up and expanded in a number of contract laboratories in the SVCP. Parallel experiments in chickens are also underway to determine the effect of an avian Type C viral vaccine on Marek's disease.

The meetings have been increasingly useful as the contract and other collaborating groups have taken advantage of opportunities to meet, discuss and exploit new findings. The multidisciplinary approach to complex research problems as a result become obvious to the Segment scientists.

In terms of the original objectives, the meetings have been highly successful in promoting collaboration and have stimulated interest and productive effort on the part of the participants. As a result, the Solid Tumor Virus Segment has been able to achieve on a voluntary basis a highly integrated program in which the contract scientists are able to move quickly to evaluate, confirm and exploit promising developments as they occur, thus avoiding long delays and needless duplication of effort prior to publication of new findings. The free interchange of information and better exchanges of the program resources have in no small measure contributed to some of the significant developments in the Segment program in the past three years. These include the isolation of three new primate Type C RNA viruses, including RD114, new insights and approaches to the Marek's disease problem, and a number of viro-immunoprophylactic developments (vaccines and interferon) for the prevention of murine and avian cancers which hopefully could be applied to the Marek's disease problem and to human cancer.

Atlantic Coast Tumor Virus Group (ACTVIGR)

The Atlantic Coast Tumor Virus Group was formed to provide an opportunity for investigators located in the eastern region of the country to discuss research activities of mutual interest. Its objectives are to promote exchange of information on current concepts and progress and to maintain integration of the research effort within the Program. The informal atmosphere of smaller discussion groups is conducive to active exchange among participants with special research interests.

Meetings are held under the chairmanship of Dr. Fred Rapp, who contributes his time to make these gatherings possible at facilities offered by

different contractors. Attendance has been limited to one day, and each participant arranges his own travel. The constraints imposed by time and space require some limitation on attendance. Accordingly, selection of specific areas of research involving several laboratories is required in order to best achieve the objectives of these meetings. The various ramifications of an area are presented by different investigators drawing on their own and supporting data, thereby providing the basis for amplification through the ensuing discussion. Participation has not been restricted to scientists within the SVCP. Contributions from others have been invited to provide more comprehensive coverage of current research.

Arrangements were made by Dr. Fred Rapp to hold the first ACTVIGR meeting at Pennsylvania State University, Hershey, Pa., on March 22, 1971. The topics discussed were of general nature reflecting the broader aspects of Program. Dr. David Yohn arranged facilities for a meeting on June 7, 1971, at Ohio State University, where those attending considered the current knowledge on relationships between herpesvirus type 2 infections and carcinoma of the uterine cervix.

The first ACTVIGR meeting in 1972 was held on January 11, at the Institute for Cancer Research, College of Physicians and Surgeons, Columbia University, New York City. Dr. Sol Spiegelman was host for this meeting to discuss molecular approaches to viral oncogenesis. The meeting was in the form of a workshop at which current investigations and anticipated future studies were discussed. Attention was directed to the nature of the DNA product of reverse transcriptase activity; a reevaluation of the quantitative relationship between the virion RNA and the DNA synthesized; characterization of the polymerase, and of the RNA template; and problems in identification of the enzyme in human neoplastic tissues.

Dr. Joseph Pagano served as host for a meeting held at the University of North Carolina at Chapel Hill on June 6, 1972. Participants involved in the study of herpesviruses were invited to discuss several possible mechanisms whereby infection by these agents might effect neoplastic transformation: direct transformation by a herpesvirus, activation of covert RNA tumor virus infection, and stimulation of host immune processes resulting in the activation of preexisting RNA tumor virus infection. Presentations provided current information on EBV, Herpesvirus saimiri, Marek's disease virus and related topics as a basis for further discussion.

Conference and Workshop on Cellular Immune Reactions to Human Tumor Associated Antigens

On June 8 and 9, 1972, the Immunology-Epidemiology Segment, SVCP, held a conference on cellular immunity to human tumor antigens. Scientists from the Special Virus Cancer Program and other invited investigators from the United States and Europe presented their recent results using a variety of *in vitro* and *in vivo* assays. After the formal presentations, the speakers and other participants discussed in depth the importance of each assay and associated technological problems. Many methodological and interpretative problems were identified. The participants agreed that

an exchange of tissue culture cell lines and other materials among the laboratories was very important and would accelerate progress in this field. There was insufficient information presented to determine which assay or assays would be most useful in monitoring patients' response to conventional therapy or to immunotherapy. The proceedings of this conference will be published by the Journal of the National Cancer Institute.

Conferences on Biohazards in Virus Research

The Office of Biohazards and Environmental Control sponsored two conferences on Biohazards in Virus Research--one at the National Cancer Institute in April and the other at Philadelphia in May in conjunction with the 72nd Annual Meeting of the American Society for Microbiology. These meetings were undertaken to acquaint investigators with current information on environmental control and thereby share important knowledge and technology gained through government supported research. The Minimum Standards of Biological Safety and Environmental Control were discussed in detail at the NCI conference. Representatives from fifty-three contract laboratories evaluated the potential impact of the proposed standards on their laboratory operations. As a result of this meeting, suggestions for improvement of these standards were made and, after critical review, were formalized.

NATIONAL CANCER INSTITUTE - FREDERICK CANCER RESEARCH CENTER

On October 18, 1971, President Nixon announced that the scientific laboratories at Fort Detrick would be converted to research on the cause, prevention, and treatment of cancer. In preparation for this expansion of NCI facilities, the Viral Oncology Area planned a comprehensive research program to augment existing cancer projects and to pioneer new areas of research. The overall program to be carried out at the new Frederick Cancer Research Center will be the responsibility of Litton Bionetics, Inc., recently named as the prime contractor for this project.

One of the primary tasks to be initiated will be the large scale production of oncogenic and suspected oncogenic viruses to meet research needs on a continuing basis. This effort will include the preparation of highly concentrated avian, murine, feline and/or other viruses for which established protocols exist and large-scale production has previously been demonstrated. In addition, the workscope includes developmental research to enhance virus production of those oncogenic or suspected oncogenic viruses for which there are no effective protocols and diagnostic reagents for the detection of viral and subviral components of selected oncogenic agents.

When the President visited Fort Detrick, he stated that it was his desire for this facility to become an internationally known laboratory. For this reason, the Frederick Cancer Research Center will have an Advanced Systems Laboratory, specifically designed for tissue culture, virological, biochemical, and immunological studies by NCI investigators and distinguished foreign scientists invited to participate in collaborative research programs.

The contractor will be responsible for developing and implementing a biohazard and environmental control program to insure the safety of laboratory personnel and the local community while preserving the integrity of all research activities. This responsibility includes the operation and surveillance of all containment systems, as well as maintaining approximately 20,000 square feet of laboratory, animal holding, and office space.

Pending the acquisition of equipment and renovation of laboratories, it is expected that the Frederick Cancer Research Center will be partially operational by October. By the end of the first year all major viral oncology tasks will have been initiated.

4. Projections:

Last year, the Viral Oncology Area set forth a long range research plan for the identification and control of virus-induced cancers of man. Studies within the following broad categories have already been implemented and will be expanded in the coming year:

a. Virus (or virus-expression) - tumor relationships

(1) Model Studies. Studies on animal, RNA and DNA, tumor viruses, known to cause malignancies in several mammalian species, will be continued. The results of these studies have already provided important information about tumor viruses that is applicable to the isolation and identification of human agents. Special emphasis will be given to determine the characteristics of several newly-isolated primate viruses. This work will remain an integral part of the Program.

(2) Human Studies. Efforts to identify viruses or detect virus expression in human tumors have been underway for some time. Because of this year's successes in isolating candidate human viruses, the Program will continue to increase its activities in the search for viruses which induce malignancies of man.

(a) To identify and isolate candidate viruses or subviral products in leukemias, lymphomas, sarcomas, and carcinomas (breast).

(b) To identify and isolate candidate viruses or subviral products in lung, colon, and other carcinomas.

(c) To develop methods for the detection of high cancer risk groups, i.e. individual susceptibility or predisposition to transformation by human viruses.

(d) To extend present and develop new methods for the successful propagation of significant amounts of human candidate viruses.

(e) To extend existing and develop new methods to induce tumor virus or virus expression in "normal" cells.

(f) To develop suitable reagents and to modify existing immunological and biochemical methods for mass diagnostic screening for candidate viruses.

(g) To characterize, biologically and biochemically, presumptive viral agents.

(h) To increase emphasis on understanding the relationship of environmental agents (e.g. chemical carcinogens) as co-factors in viral carcinogenesis. This represents a

major expansion of programs requiring combined skills of the Viral Oncology and Chemical Carcinogenesis Areas.

b. Molecular Studies

Major advances in the understanding of the molecular pathways of tumor virus replication have been made within the past year. They have already provided the basis for new, extremely sensitive methods for the detection of oncogenic viruses or virus expression. It is now possible to characterize agents detected in specimens of human cancer patients in terms of their content of high molecular weight RNA and of RNA-dependent DNA polymerase. Specific hybridization procedures already provide a method for further investigation of host-cell-virus relationships which have been extended into the study of human cancers. Preliminary results offer strong supportive evidence that certain human tumor cells contain genetic information related to that found in known oncogenic viruses.

(1) Basic Studies

The Program will continue to broaden its activities for detecting, identifying, and characterizing the spectrum of enzymes and their products required by tumor viruses for replication and/or transformation.

(2) Applied Studies

As knowledge of the fundamental molecular events in virus-cell interactions mounts, the Program will continue to apply this information to the study of human cancer as follows:

(a) To identify and characterize similar enzymes or enzymatic activities within normal and malignant human cells.

(b) To develop highly sensitive methods for the detection of virus or virus activity in human cells.

(c) To develop a rational basis for therapy or prevention by exploring various approaches to blocking of viral replication and/or tumorigenesis at the cellular and subcellular levels. The therapy could be directed at any or all of the stages of cell transformation beginning with cell infection by a tumor virus.

Ultimately these approaches will require an intensified program to develop drugs, anti-enzymes, gene repressors, or inhibitors effective at the molecular level. This represents a major expansion of effort requiring the combined skills of the Viral Oncology and the Chemotherapy Areas.

c. Immunological Studies

Immunologic research has provided extremely sensitive techniques for detection and characterization of tumor viruses, viral antigens, and changes in surface membranes of tumor cells. These studies have also contributed to an understanding of the role of immunological mechanisms in host-tumor and host-virus interactions which provide a rational approach to the prevention and treatment of cancer.

(1) Basic Studies. Investigations of selected model systems, representing tumors induced by Type C, Type B, and Herpestype viruses, will be extended to further identify, characterize, and determine the viruses, viral antigens, and membrane antigens of tumor cells. The studies include development and application of improved techniques to detect cellular alterations induced by tumor viruses alone or as the result of interaction with other environmental agents. Increased emphasis will be placed on research on spontaneous or naturally occurring tumors in model systems relevant to human cancer, as a basis for a rational approach to prevention and treatment.

(a) To study cellular and humoral immune mechanisms and to determine their relative significance in host recognition of and response to tumors and/or tumor viruses.

(b) To develop methods to enhance host response to tumors or tumor virus antigens.

(2) Applied Studies. As basic research provides the framework for identification and characterization of viruses, viral antigens, and cell membrane alterations in human cancers, immunological methods will be applied:

(a) To relate candidate human viruses to known oncogenic agents.

(b) To identify and characterize intra- and inter-species viral antigens which are present in known mammalian tumors, as probes for detecting human tumor viruses or viral antigens

(c) To determine the presence of cross-reacting antigens in various human tumors.

(d) To launch large-scale seroepidemiological surveys which will define high risk populations.

Clinical studies will be directed toward understanding and manipulation of immune mechanisms in human cancer as a basis for:

(a) Development of vaccines from identified and

fully characterized human tumor viruses.

(b) Determination of the role of host immune responses in tumor recognition and rejection.

(c) Application of (1) and (2) in the prevention and control of human cancer.

Application of the results of these studies to human cancers will require the coordinated skills of the Viral Oncology and General Laboratories and Clinics Areas.

d. Test Systems

In vitro and in vivo (animal) test systems will be carefully selected to evaluate the work outlined in the previous research areas:

(1) To determine the oncogenic potential of candidate human viruses;

(2) To develop bioassay systems for testing viral, and viral/chemical carcinogens;

(3) To begin vaccine (conventional or other) testing and immunization programs;

(4) To begin therapy testing programs;

(5) To explore special animal tumor systems, especially in primate species particularly relevant to human cancer;

(6) To develop and maintain well-characterized cell culture lines and animal stocks (small mammalian and primate species).

Many of these systems will be developed at the National Cancer Institute's Fort Detrick facility.

e. Resources

Since research efforts undergo continual change in emphasis and scope as new leads emerge, a variety of resources will have to be developed, maintained, and coordinated.

(1) Human Resources - collection and storage of serum and tissue specimens, integration of data on clinical records, storage and distribution; computerization, coordination of specimen collection, storage, and distribution;

(2) Animal Models - maintenance of various mammalian animal colonies for basic research and special studies;

(3) Reagent Production - large scale production of animal tumor viruses for basic research; production of standardized lots of purified viruses; and production of high quality diagnostic reagents;

(4) Candidate Human Virus Production - intensive developmental research effort to isolate and produce human viruses;

(5) Biohazards Control and Containment - controlled environment facilities are required for research on known oncogenic viruses and candidate human tumor viruses as well as for maintaining animal colonies which are protected from extraneous infections.

To fulfill the continually increasing need, resources have been placed under the control of a new Office of Program Resources and Logistics. Within the coming year, a prime contractor may be required to assist in the expansion of this important task.

B. SUMMARY REPORTS

1. OFFICES OF THE ASSOCIATE SCIENTIFIC DIRECTOR FOR VIRAL ONCOLOGY

SUMMARY REPORT

a. OFFICE OF BIOHAZARD AND ENVIRONMENTAL CONTROL

The Office of Biohazard and Environmental Control conducts research pertaining to the physiological and environmental factors that alter the hosts susceptibility and response to oncogenic and non-oncogenic viral infections. It also evaluates and develops techniques and equipment to minimize cross infection and provide adequate environmental controls.

The Biohazard Section conducts research to elucidate the mechanisms involved in host immunocompetence and the consequence of this on oncogenesis. Furthermore, understanding is being sought of the biochemical factors that lead to the induction of malignancy and how best to detect and modify these inductive factors. Physiological imbalances, induced by controlled stress are being examined in in vivo and in vitro systems in order to assess the host response.

We have for the first time demonstrated that the virogenic markers, group specific antigens (g.s.) and RNA directed DNA polymerase, can be activated by alteration of the physiological endocrine balance. This major finding lends strong in vivo support to the concept that genetic information for tumor virus synthesis and possibly tumor formation is transmitted vertically and can be activated by definable physiological mechanism. The potential for such activation has also been noted by us to be present in certain pesticides and in relatively low levels of ionizing radiation. We have also, for the first time, demonstrated that the host can be senitized to specific viral stimuli and subsequently demonstrates such cellular immunity by blastogenic transformation of lymphocytes.

The Environmental Control Section utilizes environmental monitoring to identify sources of contamination. To assure the integrity of primary and secondary biological barrier systems, to evaluate engineering and operational parameters and their effect on experimental and personnel contamination control. Similarly, they collect and have evaluated information pertinent to biological safety.

Minimum Standards for Biological Safety and Environmental Control have been issued to all contractors within the SVCP, these are currently being implemented. We have similarly initiated a centralized sera epidemiological surveillance service for all contract operations as well as having initiated a safety training program for senior laboratory technicians and project directors. Our consultation service to contractors, in-house research facilities and grant associated programs continues. We are planning to initiate a Chemical Carcinogenesis Biohazards Control program. This latter effort should reach full operation during the next reporting period.

b. OFFICE OF PROGRAM ANALYSIS AND COMMUNICATIONS

The Office of Program Analysis and Communications (PAC) continued its major roles in the management of SVCP data and information, analytical statistical assistance in research projects, and scientific information storage, retrieval, and distribution. Some highlights are as follows:

Statistical and Data Services

Offered to all researchers in the SVCP is a comprehensive statistical service (consultation on problems of research design, data procurement, data management, and statistical analysis of survey or experimental findings). A completely automated data processing routine directed by experienced technicians maintains direct access to the main NIH computer. Consultation and planning service is also given to SVCP contractors in developing local automation systems for managing and processing experimental data.

Automated Inventories of SVCP Resources

1. SVCP Serum Bank: Maintaining a computerized inventory of serum specimens held in the Bethesda area, PAC manages the continuous data input, updating, and distribution of specimens for testing to program scientists, from repositories containing around 40,000 serum specimen units.

2. Local Inventories: Plans and installs complete institutional automated specimen inventories in laboratories collaborating in SVCP research.

3. Central PAC Inventory: PAC is promoting compatible automated systems and codes for specimen inventories in all institutions participating in the SVCP. This includes the capture and automation of complete clinical, demographic, and laboratory information on specimen donors. Goal is a central specimen inventory at NIH making available for all of SVCP the many large specimen repositories throughout the United States.

Progress Reports

A system of managing regular (triannual and annual) progress reports from all SVCP research contracts is maintained. In addition to the logistics of monitoring and procurement, PAC compiles and distributes to program scientists condensed summaries of the actual progress reports.

Scientific Information Management

The Information Unit continued to focus attention on scientific information retrieval in the area of viral oncology, and its dissemination to program scientists. Sources of information are scientific journals, books, and other notifications and summaries of current research in the field. Major contributions of the Information Unit in FY 1972 were as follows:

1. Bibliographic Service: A semi-automated system is maintained for storage, rapid search, identification, and reference print-outs covering almost any desired topic in the published literature on viral oncology.

2. Viral Tumorigenesis Report: This semi-annual publication contains indexed summaries of current pertinent research projects, thereby presenting a panoramic view of viral oncology research.

3. Report on NCI Support of Cancer Virology Grants: This quarterly report presents an organized summary of updated fiscal data on current NCI research grants in the cancer virology area and has limited distribution to NCI adminstrators. The basic information is received from the Program Analysis and Reports Section of NCI.

4. Viral Oncology Contractor Directory: This quarterly publication contains the names, addresses, and telephone numbers of contractors, principal investigators, project officers, and contract specialists within the Viral Oncology Program. Its purpose is to facilitate and expedite communications between staff members and contractors.

5. Compilation of Journal Instructions to Authors: This displays in one volume the instructions-to-authors from a majority of pertient scientific journals. It is a reference aid for research investigators in writing papers and also for the secretaries who type them. The compilation is updated and expanded periodically.

Other responsibilities of the Information Unit are: administration of library facility; collection and distribution of translations of foreign publications in viral oncology; maintainence and lending of recorded tapes on NIH seminars related to viral oncology; and continuous compilation of the SVCP bibliography containing citations to all papers published by Viral Oncology staff members and research contractors.

c. Office of the Coordinator for Ultrastructural Studies

The Virus Studies Section continues to study different aspects of the relationship between oncogenic viruses and their host cells:

a) the search for viruses in different tumors by electron microscopic examination,

b) the examination of the life cycle of oncogenic viruses of the herpes type in their host cells,

c) the study of early events in viral infection which may result in "neoplastic transformation," and

d) the study of cellular organelles in relation to the reproduction of RNA-containing viruses.

Dr. Dalton in collaboration with Dr. Szakacs, St. Joseph's Hospital, Tampa, Florida, established 15 tissue cultures from human biopsies obtained from solid tumors. Ten cell lines are fibroblastic or epithelial in appearance, and five are growing as suspension cultures containing lymphoid blast cells resembling those blasts obtained by cultivating Burkitt's lymphomas. In the majority of these lines a series of cell types from relatively undifferentiated lymphoblasts to practically mature plasma cells have been observed. Except in one instance these cells are not the original tumor cells but are thought to be "normal" cells which have developed into continuous lines as a result of the stimulus from the presence of E B virus. These cultures were screened for the presence of virus particles. In four out of five cell lines Epstein-Barr virus was found as shown by morphological examination and complement fixation tests. About 3-5% of the cells contain in their cytoplasm an aberration of the endoplasmic reticulum, known as tubulo-reticular array. It was suggested previously that these formations may represent RNA precursors of certain myxo- and paramyxoviruses. Dr. Heine in collaboration with Dr. Schaff discovered, by using ultracytochemical methods, the sensitivity of these structures to proteases. These results make it clear that the structures are not direct RNA precursors to RNA-containing viruses.

Dr. Heine in collaboration with Dr. Hinze, University of Wisconsin, Madison, Wisconsin, studied the life cycle of H. sylvilagus in rabbit kidney cells. This DNA-containing oncogenic virus of the herpes type develops in infected cells and provokes changes in these cells similar to those described previously for H. saimiri. Both viruses produce a series of changes in their host cells known to be characteristic for cytomegaloviruses, i.e., the formation of nuclear and cytoplasmic inclusion bodies. However, in contrast to the classical cytomegaloviruses the intracellular maturation of the virions under study appears to be quite unique resulting in two morphologically different types of mature virions. These results initiated a detailed comparative study between tumor producing and non-oncogenic viruses of the herpes type and their relation to the host cell. We hope

to elucidate further similarities and differences between both kinds of viruses.

Several studies which are concerned with early events in viral infection are under way in this laboratory.

Dr. Bader in cooperation with Dr. Boone, Cell Biology Section, VBB, NCI, investigated the mode of entry of RNA-containing tumor viruses into cells by using isolated membrane vesicles as a model system. The methods of membrane isolation have not proven adequate thus far to answer the questions, and new procedures for isolating intact surface membranes are under investigation.

Dr. Suskind continued to study the intracellular mechanism of infection with Rous sarcoma virus during the eclipse phase, especially events which occur within the nucleus, by quantitative light and electron microscopic autoradiographic techniques. He succeeded in showing differences in both morphology and function between nucleoli of RSV-transformed, newly infected and uninfected cells with respect to the rate of their recovery from the effects of low doses of Actinomycin D. The results suggest the formation of new binding sites of Actinomycin D to specific DNA sites in nucleoli of transformed and newly infected cells. These experiments will be expanded using non-transforming, Rous-associated virus and thermo-sensitive mutants as well as protein and polysaccharide precursors.

Dr. Heine in collaboration with Dr. Beaudreau, Oregon State University, Corvallis, Oregon (Contract #NIH-NCI-71-2175) initiated a study to examine the fate of virion RNA after infection. In order to study the fate of viral RNA in infected cells purified MC-29-virus was prepared containing H^3-uridine at high specific activity (1-2 X 10^5 cpm/ug RNA). Cells infected with virus thus labeled have been examined 1-8 hrs. after infection and the label was recovered from a polysome fraction. Fractions that contain label will be examined in the electron microscope to confirm the presence of polysomes.

Dr. Bader studied the inhibition of mitochondrial RNA polymerase in mammalian and avian cells by ethidium bromide and observed morphological alterations by electron microscopy in mitochondria of chick embryo, rat embryo and mouse spleen and thymus cells (JLS-V5) after exposure to the drug. The effects of ethidium bromide were reversible; after its removal the cells returned to normal within a few days with respect to their morphology and growth characteristics. Chick embryo cells which had been previously treated with ethidium bromide were infected with Rous sarcoma virus and were then examined for transformation and virus production. Drug-treated cells became transformed and produced virus as seen by electron microscopy. The results of these experiments show clearly that the mitochondrial DNA template is not involved in the synthesis of Rous sarcoma virus.

Dr. Dalton has studied the details of the replication of Type B (mouse mammary tumor virus) and type C (avian, murine and feline leukemia-sarcoma viruses) particles. The results of these high resolution electron

microscopical studies demonstrate that newly formed particles have a much more precise morphology than older particles. They also indicate that the type C particles so far studied have a morphology characteristic for the species in which they are indigenous. When chrome osmium is used as a fixative, murine type C particles at the budding stage possess a relatively thick (100 Å) and distinct outer component of the developing nucleoid whether the virus is replicating in mouse or human cells. In budding feline type C particles this layer is thinner (50 Å) but still distinct. Type C virions growing from ESP-I (human) cells do not exhibit a clearly separate layer while type C virions growing from RD-114 cells have a distinct thin layer similar to the feline type C virions.

d. Office of Program Resources and Logistics

The Office of Program Resources and Logistics within the Office of the Associate Scientific Director for Viral Oncology is responsible for the review and scientific management of collaborative research contracts providing resources and logistical support to the Special Virus Cancer Program and the Viral Oncology Area. This Office was established during this fiscal year to centralize the scientific administration and management of research resources and logistical functions and to unify these activities within the Office of the Associate Scientific Director. In this way individuals responsible for coordinating these support activities could provide to the entire Program with an awareness of the overall scope of activities. This would avoid any special consideration to a particular area, any unnecessary duplication of effort, and the appearance of any undesirable competition within the Program.

Many of the research investigations carried out in the Viral Oncology Area depend on the availability of clinical and laboratory materials of optimal purity, viability, and potency. Comparable studies in an integrated program of international scope, as encompassed in the SVCP, make more meaningful and rapid progress when adequate quantities of standardized reagents, cell cultures, and test animals are available. The Office of Program Resources and Logistics provides these supportive activities through various contract operations as detailed below.

To support this office and its activities, a new contract review body was established during this year, the Viral Oncology Program Resources & Logistics Advisory Group. This Group was established by the Associate Scientific Director and constitutes a standing committee to provide support and make recommendations concerning resources and logistics matters, and to conduct appropriate reviews for those contracts within the R & L area of Program. The group is chaired by the Chief, Office of Program Resources & Logistics and is responsible to the Office. The membership includes representatives from the three Branches and the major areas of Viral Oncology.

Because of organizational changes in administrative management of collaborative research contracts, a variety of contracts formally within the R & L Segment and other segments within SVCP became the responsibility of the new Office of Program Resources & Logistics. These contracts represent three general areas of activities and include the following:

1. Activities directed toward production of virus and viral reagents, virus monitoring, and characterization.

2. Contracts concerned with acquisition, collection, storage, inventory, and distribution of human resource specimen material.

3. Contracts concerned with animal resources, including production of pathogen-free and germ-free species of animals, breeding of primates, maintenance of animal colonies, and containment-type holding facilities.

Another activity of the OPRL is the preparation of an annual catalog listing and describing the research resources available to collaborating laboratories within the Program. Usually the information provided for each item includes origin, processing procedure, degree of purity, and infectivity titer or other measures of biological activity. Additionally, in collaboration with the Office of Program Analysis and Communication, the OPRL is concerned with the development of a computerized central inventory for the sera, tumor tissue, cell outgrowths, and other human specimen materials continuously being acquired by the Program. The central inventory will greatly facilitate matching investigators requests for human materials with specimens available, regardless of the geographic location of the repository or laboratory at which it is stored.

During this past year in anticipation of an expected increase of the overall Program in the future and the limitation of personnel available, consideration was given to the establishment of a prime contract as a mechanism for dealing with resources and logistical support for Program. With this in mind, an advertisement was published in the Commerce Business Daily on November 8, 1971 requesting resumes of experience and capabilities. An Ad Hoc review committee under the chairmanship of the Chief, OPRL was established to review and evaluate the responses obtained. This Ad Hoc group questioned whether, in view of the diversified and specialized elements under the project contract, any of the respondents had demonstrated requisite qualifications. Additionally, the Ad Hoc group recommended a re-evaluation of project needs and suggested that issuance of a request for proposal be deferred.

As a result of these decisions the OPRL will continue to be involved in not only the general management of the resources program, but also in those daily activities required to make available to collaborating investigators necessary research resources.

Within the Office of the Chief, support is provided by two staff scientists and a secretary who assist in responsibilities for the management of the extramural contract operation.

2. Branch Reports

a. Viral Leukemia and Lymphoma Branch

The Viral Leukemia and Lymphoma Branch conducts research designed to elucidate the role of viruses in the etiology of human neoplasms, particularly leukemias, lymphomas and sarcomas. A variety of scientific approaches are used which provide a broad base of knowledge applicable to the identification and isolation of human oncogenic agents and the prevention or control of the disease as it occurs in man. More specifically, the Branch encompasses a range of scientific disciplines including molecular biology, genetics, immunology, biochemistry, pathology and cell culture techniques. In the past year, the emphasis has been away from model systems to the more direct study of human materials.

The Section of Molecular Biology seeks to obtain comprehensive knowledge of the biology and biochemistry of sarcoma and leukemia viruses and conducts quantitative studies on the interaction of oncogenic viruses and cells to determine the mechanisms of viral replication and cellular transformation at the molecular level. The Section of Viral Pathology exerts a multidisciplinary approach towards the in vivo and in vitro study of viral oncogenesis. The areas of study include virology, immunology, pathogenesis and the interferon system, and are pursued emphasizing several viral induced and spontaneous leukemias and sarcomas. The Section of Immunology examines the antigenic nature of oncogenic viruses and the induced tumors as well as the immune response of the host to viral infection and tumor development. The Section of Tumor Viruses is concerned with defining in detail the biological and biochemical properties of tumor viruses in order to understand how they may be applied to the search for human tumor viruses. A "helper" assay to "rescue" oncogenic virus information is currently being applied to human cell systems. The Section of Genetics is concerned with genetic factors of both the tumor virus and the host it infects that are involved in the oncogenic process. Particular emphasis is placed on the viral genes involved in oncogenesis and cellular "susceptibility" genes, particularly those genes of man that predispose individuals to the development of cancer. The Office of the Chief coordinates the research of the various sections by recognizing the scientific freedom of the individual investigators. The office is responsible for establishing collaborative efforts with investigators in other areas of NIH and elsewhere such that information derived from studies within the Branch is constantly being applied in investigations leading to a better understanding of the etiology of human neoplasia.

Potential RNA containing tumor viruses have been recognized by a number of methods based on biological, biochemical, and immunological properties. More recently the reverse transcriptase has provided another potentially extremely sensitive method for virus detection.

The discovery that certain RNA tumor viruses have an enzyme capable of transcribing the viral RNA back into DNA has lead to the possibility of using extremely sensitive biochemical probes to search for evidence of viral etiology of cancers, and especially, cancers in man. Some of the potential applications to the etiology and control of human cancers are:

1. The use of synthetic DNAs produced from the viral RNA to search for complementary RNA in human tumors by DNA-RNA hybridization techniques.

2. The use of highly effective synthetic templates and optimal enzymatic conditions to search for viral reverse transcriptase in human tumor cells.

3. The use of specific antiserum prepared against the purified viral enzymes to identify individuals that have been exposed to the viral enzyme. It is reasonable to expect that the antibodies to viral specific proteins may persist for much longer periods than the virus itself would persist.

Each of the above approaches are being actively followed by members of the Viral Leukemia and Lymphoma Branch.

Following the initial reports of RNA-dependent DNA polymerase in the virions of certain RNA tumor viruses, it was important to see if the enzyme was specifically restricted to tumor viruses and whether it was specifically restricted to tumor cells. All of the oncogenic RNA viruses tested so far have been found to have DNA polymerase, as indicated both by endogenous reaction using the viral RNA and by synthetic polymer-stimulated reactions, using such templates as poly rA.rU, poly rI.rC and poly rA.dT. The non-oncogenic RNA viruses have shown no evidence of this enzyme activity. Two apparent exceptions were found. The first, visna virus, produces a chronic, progressive, neurological disease of sheep but has, heretofore, not been associated with tumors in sheep. The second major exceptions are the group of "foamy" viruses. These RNA-containing viruses are frequently found in healthy as well as diseased monkeys, cattle and cats, and they have not yet been associated with any disease. Visna and "foamy" viruses, then, are apparent exceptions to the rule that only tumor viruses contain reverse transcriptase. Whether visna and the related viruses of sheep and the various "foamy" viruses are potentially oncogenic in their natural hosts remains to be resolved.

The polymerase, as an antigen, like the gs antigen has both species specific and interspecies characteristics. Tumor-bearing animals can make antibody to the viral polymerase and some sera appear to be more broadly reactive than others. The murine polymerase has been partially purified and used to produce an antibody in rabbits. The antibody, an IgG immunoglobulin, is directed against the enzyme and not against the template. The antibody to the mouse leukemia virus polymerase will also

inhibit the enzymatic activity of hamster, rat and cat leukemia virus polymerase. Thus, the polymerases from different mammalian tumor viruses are antigenetically related. However, the crosses with other mammalian C-type viruses are only partial crosses allowing precise identification of the species of origin of an unknown C-type virus. The mouse mammary tumor virus, visna, and the avian leukemia virus polymerases are not inhibited at all by this serum. The antibody to the avian virus polymerase inhibits all the major avian C-type viruses, but not any mammalian C-type virus polymerase.

Two new C-type viruses of primates have recently been described by Kawakami and co-workers. One is from a woolly monkey fibrosarcoma; the other is from a gibbon ape lymphosarcoma. Both have a polymerase with the characteristic properties of tumor viruses and can be classified as C-type based on morphology. They also have the biological properties of C-type viruses and also have a cross-reacting gs antigen. The polymerase antibody studies, however, show a very weak or absent cross reaction with antibody to rodent or cat virus polymerase. Both the murine and feline C-type viruses can grow in primate cells without losing the immunologic specificity of their polymerase. These findings provide additional evidence that the polymerase coded for, at least in part, by the viral genome. From the experiments on polymerase inhibition, the woolly monkey and gibbon ape viruses appear not to be contaminating rodent or feline C-type viruses and appear to have a polymerase that is distinguishable from that of the C-type viruses of lower mammals. An antiserum prepared to the gibbon C-type polymerase inhibits gibbon and woolly virus enzyme well, but only poorly crosses with the rodent and feline previously described C-type virus polymerase.

The isolation of C-type viruses from both old world and new world monkeys from naturally occurring tumors greatly strengthens the possibility that related viruses will be directly isolated from human tumors. Several reports of C-type viruses in human cells have been presented in the past year. While some of these are more reasonable candidates than others, no proven "human" C-type is yet available. Until such viruses are found, the C-type viruses of primate origin should provide the best probes for the detection of C-type information in human cells.

In 1969, it was proposed that the cells of most or all vertebrate species contain C-type RNA virus genomes that are vertically transmitted from parent to offspring. Depending on the host genotype and various modifying environmental factors, either virus production or tumor formation, or both, may develop at some time during the life of these animals or in their cells when grown in culture. The evidence for this concept was derived both from cell culture experiments and from a variety of seroepidemiologic studies and was presented as a unifying concept that would be consistent with the facts as they were known at the time.

In the two years that have followed, a great deal more evidence has accumulated that provides strong support for the general theory. One

particular prediction that was made was that the genetic information for making an RNA tumor virus, being present in a repressed form in all cells, would be potentially inducible by carcinogenic and/or mutagenic agents. Recent evidence from single cell clones of mouse embryo cells of both the high susceptible strain, AKR, and the low susceptible strain, Balb/c, indicate that every cell clone in culture does contain the information for producing a C-type virus. Infectious virus can be induced from clonal lines of mouse, rat, and Chinese hamster cells, normal as well as transformed, which provides dramatic support for the original hypothesis.

The oncogene hypothesis makes several testable predictions. The first is that all somatic cells should contain the genetic information to produce a C-type virus that can be detected by using the DNA product made from C-type viral RNA of that particular species. For example, normal cat cells should have in their DNA a complete copy of cat leukemia C-type virus RNA, and the hamster should have in its DNA the genetic information for making a hamster C-type virus. A second and, perhaps, stronger prediction is that transformed cells, whether transformed by exogenously added tumor viruses or by radiation, chemical carcinogens or even "spontaneously", should contain new messenger RNA sequences that are not found in normal cells and that are common to all transformed and tumor cells of a particular species. This information should also be contained in the C-type tumor virus of that species. The new messenger RNA would be the product of the oncogene and in turn code for the production of the transforming protein(s). A third prediction is that it should be possible to isolate cell mutants that, at the nonpermissive temperature, because of a temperature sensitive repressor, would be superinducible or would possibly spontaneously produce C-type virus without exogenous inducer. A final prediction, if the general hypothesis is correct, and C-type viral information has been a stable part of the evolution of vertebrates, would be that the C-type viruses derived from closely related species would be closely related to one another in the antigenic properties of their characteristic proteins. Two such proteins are now available--the major group specific antigen and the reverse transcriptase. The isolation of C-type viruses from reptiles, birds, as well as mammals would suggest that they have evolved as the organism has evolved for many millions of years and that the species specific proteins will have evolved in much the same way that serum albumins, globulins, and other proteins have evolved. The genetic relatedness of the group specific antigens and the reverse transcriptases may well, then, be used as an index of the genetic relatedness of the species from which the C-type virus was derived. Obviously, those viruses derived from higher mammals, and especially primates, will be the most related to the viruses that come to be obtained from man. The VLLB is concentrating on the primate C-type viruses, because they should have enough genetic relatedness so that an antiserum produced to the purified polymerase or the purified group specific antigen should show some ability to recognize C-type viruses isolated from human tissues.

Other Research Developments in the Branch

Characterization of continuous, contact-inhibited mouse cell lines from Balb/c and NIH/Swiss embryo cells has provided excellent model systems for study of the effects of tumorigenic viruses both in vitro and in vivo. These cell lines, and a wide variety of well-characterized subclones from them, are supplied to numerous investigators throughout the world, and have become standard cell lines for biochemical and biological investigations of cellular growth control mechanisms.

New types of MSV-transformed cells, the nonproducer cells, have been discovered. These cells are morphologically transformed and are highly tumorigenic, yet they lack all the known antigens of the murine sarcoma-leukemia complex. The sarcoma genome can be readily rescued by the addition of "helper" leukemia virus. These nonproducer cells provide a very good model for the study of naturally occurring cancers. Viral specific information can be detected by nucleic acid hybridization at less than 1% of the level in the transformed virus producing cells. Optimal techniques for detection of viral information in these cells are being applied to studies on the detection of viral information in human tumors and human tissues.

Studies on the S+L- cells developed by Bassin, et al have revealed that the particles they produce have only the main group specific (gs) and the interspecies antigen. while the other gs antigens seem to be missing or radically different. Type specificity of the S+L- virus is also not related to previously described MuLV groups. The S+L- particle itself contains a neatly reduced amount of reverse transcriptase; the S+L- cells are also deficient in this enzyme. A significant lack of homology between MuLV and the standard coated MSV was seen when mixtures of MSV-MuLV (4:1) were examined by reciprocal cross-hybridization with the respective DNA reverse transcriptase products. Additionally, atypical large molecular weight nucleic acids may be a natural component of MSV as well as previously observed ribosomal and transfer RNA species.

A major advance has been the development of virus stocks which have a significant (4- to 50-fold) excess of the transforming MSV over its associated murine leukemia "helper" virus (MuLV). With a favorable MSV excess the isolation of cells transformed only with MSV and the study of MSV genome itself are greatly facilitated. The result has been the development of numerous cell lines that are "transformed" by MSV but have only a minimal expression of the tumor virus information. The virus from these cultures with an excess of sarcoma virus should provide a valuable probe for the search for sarcoma virus specific information in apparently "virus-free" tumors.

Radiation leukemia virus, a "natural" virus induced from C57B1 mice has been found to be able to replicate, albeit with great difficulty, in 3T3 cells. Because the radiation leukemia virus is able to grow much better in S+L- transformed 3T3 cells, it may be that the great majority

of naturally induced C-type viruses existed as MSV complementation requiring variants. The isolation of new natural viruses may require the above model techniques. An obvious extension that is actually being investigated is the isolation of human cells infected only with MSV and the attempted induction from them of the postulated endogenous human helper C-type virus. "Revertants" of MSV transformed that have lost partial or complete virus extension have been obtained from a number of systems. These cells also have lost tumorigenicity. In some cases the input oncogenic information appears to be lost; in others it is suppressed. The latter situation provides an excellent opportunity for the study of the mechanism by which tumor virus information is repressed.

A new strain of murine sarcoma virus isolated from a B/W mouse is accompanied by a non-cytopathogenic "helper" virus required for release of infectious virus. Unlike other strains of sarcoma virus, the new MSV retains the ability to express the murine gs-1 antigen in hamster and cat cells. The presence of a convenient antigenic marker is useful in studies involving trans-species rescue of the MSV genome using putative "human" C-type viruses. Marked mouse strain differences are noted in the response to this MSV strain. In Balb/c and C3H mice tumor regression, virus titers, viral neutralizing and cytotoxic antibody titers are correlated. But in B/W mice, the tumors persist despite very high titers of neutralizing and cytotoxic antibodies, and absence of detectable infectious virus.

The combined use of immunology and electron microscopy has greatly increased the sensitivity and specificity with which virus specific and virus directed antigens may be localized. In addition to ferritin and southern bean mosaic virus coupled to hybrid antibody, tobacco mosaic virus (TMV) has been utilized and established as a third marker for immuno-electron microscopy. Fragmented TMV (50 mμ) can be used with the other two markers for conventional electron microscopy, since these three markers are clearly distinguishable from each other by their shapes and specificities. Thus, the use of these three different markers opened a way to examine the relationship among different antigenic sites on the surface of the virus and the virus-containing cells. During virus budding, it is seen that the C-type virus incorporates cell surface components into the viral envelope.

Micro techniques for the isolation of temperature sensitive leukemia virus mutants have been developed. By these methods, it has been possible so far to isolate 27 temperature-sensitive leukemia virus mutants from clonal stocks of Kirsten and Rauscher leukemia viruses. Each mutant transmits to new cells with efficiency comparable to that of wild-type MuLV at the permissive temperature, but is at least 4-5 logs less efficient than wild-type at forming XC plaques at the nonpermissive temperature. The mutants all have very low rates of reversion to wild-type. Temperature sensitive sarcoma virus mutants have also been isolated. With these it is hoped that the viral protein directly responsible for the maintainence of the transformed state can be studied.

A continuous cell line, HBT-3, was established in culture from a human breast adenocarcinoma. The cells are epithelioid in appearance, grow rapidly, and form multilayered colonies. HBT-3 cells have a cloning efficiency of approximately 70% and an abnormal karyotype. Preliminary experiments with this cell line suggest the possible presence of 60-70S RNA and an enzyme that is similar to the known viral reverse transcriptases.

By nucleic acid hybridization, it has been possible to detect C-type viral specific RNA from every mouse cell line tested to date, including such lines as Balb/3T3 and NIH/Swiss mouse embryo fibroblasts (NIH/3T3). Cell lines transformed by SV40 and Kirsten or Moloney sarcoma virus show increased levels of hybridization. The finding of partial expression of murine C-type information in "normal" mouse cells not treated with inducing agents suggests possible post-transcriptional control of the expression of the endogenous virus information.

Rauscher-MuLV reverse transcriptase is denatured by, and renatures upon removal of, guanidine hydrochloride (GuHCl). The enzyme is composed of one polypeptide chain of molecular weight approximately 70,000 - 80,000. The renatured enzyme obtained from an agarose column run in 6M GuHCl and reducing agent still possesses RNA and DNA directed DNA polymerase activities associated with the native enzyme. The renatured enzyme reacts with antibodies specific for the native enzyme. Studies are in progress to irreversibly denature host cell polymerases but not the viral enzyme. If successful, this will provide a rapid, specific assay for reverse transcriptase in host cells.

Immunoadsorbant columns using anti-viral polymerase antibody coupled to Sepharose have been used to purify reverse transcriptase from cells and tissues. Large scale screening of human cell extracts using affinity chromatography will be undertaken when a high titered antibody directed against the primate C-type viral reverse transcriptase is available.

Continuous therapy with interferon inducers effectively suppresses several virus-induced and transplantable tumors. However, pretreatment with single doses of interferon inducers often results in marked enhancement of oncogenesis by RNA tumor viruses. Pretreatment with inducers can result in the more rapid growth of several transplantable tumors in certain systems. Several synthetic deoxynucleotides induce low levels of circulating interferon and prevent death in mice from arborvirus infections. They also enhance tumor induction by murine sarcoma virus, an effect produced by all the interferon inducers tested to date. These studies may help elucidate the mechanism of interferon induction in the animal.

AKR mice have been considered immunologically tolerant to MuLV since they are G antigen positive during their entire life span. It has become evident, however, that the kidney-eluate of untreated AKR mice contains at least two different antibodies to intraviral G antigen(s) and the Gross cell surface antigen, although no free antibodies are detected in the body fluid. These findings indicate that there may not be absolute

immunological tolerance. Immunologic studies on the behavior of malignant cells might suggest methods of treating tumor patients. The apparent absence of absolute immunological tolerance to C-type virus-associated antigens raises the question of whether it may be possible to break relative immunological tolerance to both viruses and malignant cells. In combination with studies on activation of viral genome producing antigens this may open a way to the development of immunologic methods of prophylaxis and treatment.

Controlled studies continued to demonstrate that patients with Hodgkin's disease have higher EBV antibodies than matched controls. Studies with cell-mediated immunity to a variety of antigens indicated that anergy was associated with a poor prognosis, but there was no correlation between EBV titers and general cell-mediated immunity. At least three Rhesus monkeys have been successfully infected with EBV. This was demonstrated by persistence of elevated antibody levels to the virus while monkeys given non-infectious EBV did not maintain high titers. The ability to infect Rhesus monkeys with EBV is of significance because it raises the possibility of a good model system for human studies. Rhesus monkeys have natural antibody to a virus indistinguishable from EBV at the present time, and by manipulation of the animals with inbreeding and immunological alteration, it may be possible to use monkeys as a model for the study of EBV-induced diseases in humans.

Ten sets of identical twins, one member of each pair having leukemia, were studied by at least two different immunological tests. Similar studies were performed on six sets of normal identical twins. In six of the leukemia families studied, lymphocytes from family members and unrelated donors were cytotoxic for cells from leukemic twin and not for cells from the normal twin. Delayed hypersensitivity reactions were elicited by extracts of patients' leukemic cells but not by extracts of remission cells and from the normal twin cells. Neither cytotoxicity nor delayed hypersensitivity were found in any of the normal identical twins.

Other Activities of the Branch

During this reporting period, senior investigators of the Branch published a total of 85 papers which covered various aspects of viral oncology.

Members of the Branch presented by invitation over 50 lectures to research groups in this country and abroad, and over 30 abstracts were presented at various scientific meetings. The Branch entertained approximately 150 visitors for discussions in various aspects of viral oncology; this included representatives from every major research institution in this country and from 14 foreign countries. The Branch also provided training for periods up to six months in a variety of experimental procedures to outside visitors. This training consisted of orientation in immunological, biological and biochemical procedures as well as virus handling techniques.

Many of the investigations described in the Viral Oncology portion of this report depend on the availability of clinical and laboratory materials of optimal purity, viability, potency, etc. The interaction which results in neoplasia needs several participants: the virus(es), the cell, or their already reacted product, the transformed cell. An understanding of each of the components requires highly specialized, well defined and custom made reagents with recognizable markers to serve as specific probes. Indeed, comparative studies in an integrated program of international scope, as encompassed in the SVCP, can make more meaningful and rapid progress when adequate quantities of standardized reagents, cell cultures and test animals are available.

The Resources and Logistics Activity provided viruses and antisera, human tissues, special laboratory animals (including infectious leukosis virus-free eggs), all produced, characterized, stored and distributed under various contract operations. Diagnostic services for the detection of murine, non-human primate, and cat viruses, and the viral reagents for these tests, were also provided.

In addition, several of the senior investigators within the Branch spent a portion of their time in support of the Special Virus Cancer Program. The members serve as Chairmen, Vice Chairmen, Work Group members and Secretaries of the major segments of the Program. They provide scientific guidance as Project and Assistant Project Officers on research contracts supported by the Special Virus Cancer Program.

The activities of the SVCP and the direction of the internal research program of the Branch are aimed at the common goal of the determination of the viral etiology of human cancer. It is apparent that the efforts of the Branch members have played a significant role in the progress of the SVCP to date. The broad scientific perspective developed by these investigators in their SVCP activities has also contributed significantly to the direction of the Branch program for the attainment of research goals.

The effective functioning of senior personnel in dual capacities, i.e., in-house research and program administration requires a delicate balance of effort. It must be realized through constant monitoring, that such a balance does exist and over-emphasis in either direction would be to the detriment of both programs. It has become clearer during the past year that an understanding of the suspected relationship between tumor viruses and human neoplasia requires an interaction between, among others, highly skilled molecular biologists, epidemiologists, cell biologists and physicians, along with sound and constructive administrative support, the answers will come from no one discipline alone.

2. Branch Reports

SUMMARY

b. Viral Biology Branch

The Viral Biology Branch conducts research on viral and host factors related to the carcinogenic process and on the development and evaluation of measures for control in experimental systems. Specifically, investigations are conducted to identify virological activity in oncogenesis. In defined systems, the biological interaction between viruses co-infecting the host is studied to determine the effect on tumor virus expression and on the development and course of disease in the host. Ultrastructural studies permit detection and morphological characterization of viruses associated with disease processes and the effect of viral activity on internal organization of the cell. Biochemical events related to viral infection are followed. Investigations continue on alterations in the surface membrane of cells that undergo neoplastic transformation and the immune responses which may be induced in the host against new membrane antigens of neoplastic cells. Combined chemotherapeutic and immunological measures are evaluated as approaches to the control of viral expression and the growth of tumor cells.

The Office of the Chief coordinates the research efforts conducted in the Sections within the Branch and collaborative studies with investigators in other laboratories. The Chief serves as Chairman of the Developmental Research Segment of the Special Virus Cancer Program. In this capacity he has been responsible for the administration and management of 29 extramural research contracts within the Segment program concerned with: the detection, isolation, and characterization of viruses associated with tumors in man and animals; molecular biological studies on virus-host cell relationships; the activity of enzymes within virions as these may be related to the processes of virus infection, integration, replication and cell transformation; virus nucleic acid base sequences; immunological factors activating virus expression in covert infections; evaluation of immunological approaches to the control of tumor virus infection or expression; maintenance and use of non-human primates for the study of viruses of possible etiological importance in human neoplasia; and the production of viruses and cells in quantity in support of the overall Special Virus Cancer Program. He is supported by the Vice Chairman of the Segment, secretarial assistance, and investigators within and outside the Branch who serve as Project Officers and/or members of the working contract review group. He has been apprised of developments in molecular virology by an advisor for molecular studies functioning within his office.

The Cell Biology Section specializes in investigations on the role of the tumor cell surface membrane in carcinogenesis and in the induction of cell-

mediated host immune responses to tumor cell antigens. The Virus and Disease Modification Section conducts a multi-disciplinary approach to the detection, prevention, treatment and/or control of neoplastic disease in experimental animal systems, and studies in vitro and in vivo on the interactions between oncogenic and non-oncogenic viruses which may affect the disease process. The Human Tumor Studies Section is concerned with the study of viruses associated with, or contributing to further knowledge of possible etiological relationships in, human cancer. The Microbiology Section seeks to obtain information on biological interactions in selected tumor virus-cell systems. The Experimental Pathology Section follows the progress of viral infection, immune responses, and the influence of the immune state on the development of neoplastic lesions in selected animal systems. The Electron Microscopy Section devotes its efforts to the detection of particulate viruses in tissues or cell cultures, the definition of ultrastructural characteristics of viruses and of intracellular changes associated with virus infection, the localization of antigens within cells, and support to other investigators requiring such services.

Research Developments within the Branch:

An increase in the immunogenicity of weak tumor cell surface antigens was obtained by incorporating influenza virus antigens into the cell surface membranes. Following formalin treatment to inactivate the influenza virus, vaccination of animals with homogenates of these cells gave significant protection to animals against challenge with viable cells of that tumor. These original observations were confirmed and extended to demonstrate induced immunity to SV40 transformed tumor cells and methylcholanthrene-induced sarcomas.

Dual infection of cells by an oncogenic RNA virus and a non-oncogenic virus may enhance the oncogenic response. Investigations conducted in vivo and in vitro have shown that infection by an arbovirus stimulated the production of increased amounts of mouse sarcoma virus. Somewhat similar results were obtained when a non-virus-producing line of SV40 transformed cells was infected with mouse sarcoma virus. Evidence showed activation of SV40 production, while the MSV(M) released in this line induced an altered pathology in mice. Arbovirus infection also appears to affect neoplastic cells. A lymphoblastic cell line established from a spontaneous lymphoma of the AKR strain mouse lost Gross virus cell membrane antigen and its tumorigenicity after infection with Germiston virus.

Previous exposure of mice to BCG followed by infection with MSV(M) in admixture with BCG completely inhibits tumor development. Lymphocytes from these animals, while not as effective as lymphocytes from tumorous animals, were capable of killing labeled MSV(M)-induced tumor cells as demonstrated by release of Cr 51. Studies on BCG and another non-specific immune stimulator, Corynebacterium granulosum, were extended

to animals which had been inoculated with the transplantable murine lymphoid leukemia, LSTRA, and subsequently placed in remission by treatment with BCNU. In groups of animals treated with the immune stimulators prior to relapse, 70 to 80 percent remained disease-free as compared to the 80 to 90 percent mortality observed in those groups that received only drug treatment. Similar groups of mice in remission following treatment with 25 ml/Kg of BCNU received single or multiple injections of spleen cells from normal and immune mice. All groups contained a high number of survivors. Why normal spleen cells were effective is not known. Prolonged host survival was not obtained when immune and normal spleen cells were inoculated after treatment with 20 ml/Kg of body weight of BCNU, suggesting a reduced tumor burden is essential.

An antibiotic, Streptonigrin, is highly effective in nonogram amounts in inhibiting murine leukemia and sarcoma viruses in vitro. A marked decrease in titer of Rauscher MLV recoverable from infected mice as well as an increase of survival time of these mice has been observed in groups treated with Streptonigrin. This antibiotic is interesting in that it inhibits the avian myeloblastosis virus reverse transcriptase activity.

In experiments exploring humoral factors affecting tumor growth in animals the effectiveness of immune sera in inhibiting the growth of virally-induced mouse sarcoma cells in animals was shown to correlate with the anti-cell membrane and virus neutralizing titer of a serum. Pretreatment of mice with serum from animals with progressively-growing sarcomas enhanced the growth of a challenge inoculum of tumor cells. This serum possessed no anti-cell membrane, virus neutralizing, or cytotoxic activity. Tumor cell growth was inhibited by sera from animals in which tumor had regressed and by sera from tumor-immune animals of another strain. These sera were not cytotoxic for tumor cells, but had anti-membrane and neutralizing activity. Fifty percent of the serum-treated mice that initially rejected the challenge dose of MSV-induced sarcoma cells rejected a second larger challenge inoculum given 45 days later.

A rat virus of C-type morphology, continuously released by the R-35 cell line established from a spontaneous mammary carcinoma of the Sprague-Dawley rat has been reported to have specific infectivity for cultured rat mammary gland tissue. Infected cells underwent transformation and grew to produce tumor when implanted into rats. A number of rats infected shortly after birth eventually developed tumors of possible mammary gland origin.

Experiments were conducted to define the relationship between this virus and other rat C-type viruses. Infectivity studies showed that animal species other than the rat were refractory to the R-35 virus. Immunofluorescence studies were conducted to determine cross reactions between cell membrane antigens of R-35 cells, cells of the WF-1 line originated from a W/Fu rat, and cells of the RMTL-8 line from a chemically-induced mammary tumor in a Sprague-Dawley rat. All these lines shed C-type virus.

Sera from W/Fu rats bearing WF-1 tumor reacted with WF-1 cell membranes in immunofluorescence tests. Some of these sera reacted with R-35 and RMTL-8 cells. Absorption experiments verified the presence of cross-reacting cell membrane antigens, and preliminary results of neutralization tests provided further evidence that these rat-C-type viruses are antigenically closely related and perhaps identical.

The availability of an animal host susceptible to infection by Epstein-Barr virus (EBV) would substantially aid in the study of this virus. Old World monkeys, such as the Rhesus, African green, Bonnet, and other species were found to possess a high incidence of antibody reactive with EBV-associated antigen in immunodiffusion tests. Apparently, these monkeys are infected by a virus related to EBV. However, no such virus has been isolated from these animals, nor do their lymphoid cells respond to infection by EBV as do human lymphocytes. Antibodies reactive with EBV have not been detected in New World monkeys. Bone marrow cells from the marmoset and the Owl monkey were exposed to infective EBV and monitored for transformation and production of EBV antigens. There was no evidence of infection. Whereas long term propagation of human lymphoid cells in vitro appears to be directly related to preexisting infection by EBV, a cell line of lymphoblasts, established from a carcinogen-induced leukemia of a rhesus monkey free of antibody to EBV, showed no evidence of the presence of antigens reactive with antisera to EBV. Thus, the problem of a suitable experimental animal for EBV studies and the question of the cell site and significance of infection by an EBV-related virus in the species of lower primates studied remains unresolved.

A search was undertaken for the presence of virus-like particulates in purified, concentrated fractions of milk from women from families with a history of cancer. No particulates which could be definitely described as B- or C-type were detected. Particles resembling the M-PMV recovered from a monkey mammary tumor were present in 23 of 308 specimens examined by electron microscopy. The presence or absence of such particulates did not correlate with reverse transcriptase activity in the milk samples.

Attempts have been made to activate virus release from cultured mammary tumor cells from humans and dogs by treatment with reagents known to induce virus production in mouse cells. These methods have been unsuccessful in a limited number of trials.

The Electron Microscopy Section has provided support to different investigators within Viral Oncology. Approximately 1500 specimens have been studied. Collaborative studies with Dr. John Hooks and Dr. D. C. Gajdusek, NINDS, on a new virus isolated from brain cell cultures originated from tissues obtained from a patient with Creutzfeldt-Jakob disease showed the agent to be morphologically similar to M-PMV.

Feline sarcoma virus and an associated helper virus infects cat, bovine, and human cells. A non-virus-producing infected cell system would be useful for detecting viruses in human leukemic tissues, providing helper activity to the defective sarcoma virus genome in cells susceptible to

infection by human virus. Serial passage of the sarcoma virus complex in bovine cells ultimately selected a virus population with an enhanced efficiency of infection for bovine cells as compared to feline cells. Focal areas of transformed cells have been selected and cultured. These lines shed substantial, moderate, or essentially no progeny virus. The value of these poor shedder cells as a detector system for other leukemia viruses is being explored.

During the reporting period, 26 papers, published or in press, have originated in the Branch and members of the staff have been co-authors on 10 papers resulting from collaboration with others. Members of the staff have presented by invitation 8 lectures in this country and abroad.

Other Activities within the Branch:

In addition to their intramural research activities, a number of investigators within the Branch have devoted substantial amounts of their time as Project Officers, as site visitors to laboratories conducting research under contract, and as members of Groups reviewing research contract proposals within the Special Virus Cancer Program. Dr. Michael Chirigos, Associate Chief of the Viral Biology Branch, has replaced Dr. Jack Gruber as Vice Chairman of the Developmental Research Segment. Dr. Gruber has been reassigned to a position of greater responsibility. Dr. Timothy O'Connor has acted as advisor in Molecular Virology to the Associate Scientific Director for Viral Oncology. He has coordinated studies on the inhibition of viral polymerase by rifamycin derivatives in a collaboration between NCI and the Dow Chemical Company, and has assisted in contract reviews as a member of the Developmental Research Segment Working Group. Dr. Charles Boone has served on the Immunology and Epidemiology Segment Working Group. Dr. Gary Pearson has contributed his services as Executive Secretary to the Immunology and Epidemiology Segment. In addition, other members of the Staff serve as Project Officers and participate in monitoring research contract activities.

SUMMARY REPORT

c. VIRAL CARCINOGENESIS BRANCH

July 1, 1971 June 30, 1972

Introduction

The cancerous state begins when a stable neoplastic (genetic) change occurs in one or more normal cells. This first step is attributable, according to modern theory of the genetic code, to a defect or breakdown in normal cell regulation of inherited oncogenic genes (oncogenes), the structural gene that initiates and maintains the "spontaneous" neoplastic state. The tumor actually develops from the transformed neoplastic cell as a consequence of a second step occasioned by defects or breakdowns of the host's immunological surveillance, thus allowing neoplastic cells to replicate more or less ad lib in the whole organism.

Research Objectives of the Viral Carcinogenesis Branch.

The inhouse Viral Carcinogenesis Branch and the Solid Tumor Segment's contracts program, working in close collaboration with other SVCP Branches and Segments, are engaged in comprehensive studies of the etiological factors involved in the two events described above which, along with exogenous carcinogenic factors, are critically important in the development of cancer.

Prevention or repair of the breakdowns in regulation and control at both the cell and organism level is of course our ultimate goal This requires studies of the normal cell and of the cancer cell, and of exogenous agents that impinge on or alter normal cell behavior, and the host responses to this alteration.

Our contemporary strategy is to prevent cancer first in experimental and natural animal systems and then, shortly afterwards, in man. In order to accomplish this we have developed several staging areas for collaborative research.

Specific Contemporary Targets of VCB-STS Programs:

1. To test the validity and heuristic value of the RNA viral oncogene hypothesis in humans as well as in laboratory and feral vertebrates. Very recent data (late FY 1972) provided powerful direct support for the viral oncogene hypothesis at the cellular level (*vide infra*).

2. To apply the findings and concepts generated in Target 1 to the development of better techniques capable of providing more accurate assessments of the specific structural and regulatory genes and other endogenous mechanisms involved in spontaneous neoplasia.

3. To apply new *in vitro* as well as *in vivo* carcinogenesis techniques developed in VCB and STS in quantitative assays of unknown as well as known environmental carcinogens. In the process we are studying carcinogenic (and mutagenic) agents as (a) inducers of expressions of the endogenous RNA tumor virus genes, and (b) co-carcinogenic agents acting in concert with additional overt copies of infectious (but nontransforming) RNA tumor viruses, the latter serving as critical determinants of *in vitro* neoplastic transformation.

4. To utilize the remarkable increase in sensitivity provided by cells infected with nontransforming RNA tumor viruses to screen for and quantitatively assay for carcinogens suspected to be extensively present in the random ecologies in which highly developed societies live.

5. To apply newer knowledge and techniques in attempts to prevent oncogenic transformation and tumors and conceivably also to find ways to reverse the oncogenic state at the cellular level.

6. To make use of recent findings by STS-SVCP scientists which show that the immunological system exercises critical controls over tumor cell growth in vivo. Cell mediated and humoral responses to tumor cells have been demonstrated.

7. To continue the search for overt representatives of the postulated RNA tumor virus of man; at least one very good candidate has been isolated by McAllister and his associates. This virus grows well in culture and has been characterized as a mammalian type C RNA virus. Thus concepts and techniques developed from our extensive natural history studies of similar viruses in animal systems are proving very useful in similar studies of human cancer.

8. To develop comprehensive epidemiological and laboratory studies of human cancer in a large urban population (Los AngelesCounty), including surveillance not only of human cancer incidences and cancer virus expressions, but of the similar type C viruses found in several species of feral animals present in large numbers in the same ecosystem. Identification of carcinogenic factors within the Los Angeles ecosystem and their influence on cancer incidence are major goals.

New Discoveries Relating Specifically to the Eight Specific Research Targets of VCB and STS

I. In support of the viral oncogene theory.

The reports late in 1971 by Rowe and Klement and their associates that all clones and subclones of mouse and rat cells can be induced by mutagenic and carcinogenic chemicals (BrdU, IdU, 3MC, DMBA and others) to replicate infectious type C RNA viruses can only be explained by universal genetic transmission of the complete RNA type C genome. Similar observations by Aaronson and Todaro (VLLB) in all clones of nonpermissive BALB/c and Swiss 3T3 mouse cells provided simultaneous confirmation of these exceedingly important findings. Entirely compatible data were also supplied for hamster cells by Kelloff and Freeman, and for chicken cells by Weiss, Hanafusa and Vogt. We interpret these new data, as well as recent reports of type C viral molecular RNA sequences in virus-free normal and tumorous tissues of mice and chickens (STS contractors Green, Duesberg, Bishop and Levinson) as direct evidence for inheritance of the type C RNA genome by all the cells of these vertebrates.

II. A. Endogenous mechanisms. Mendelian studies of endogenous virus expressions.

Mendelian genetic studies by Rowe and Hartley, Lilly and Meier and their associates of RNA tumor virus genomes in inbred mouse strains clearly established that natural (endogenous) gene expressions of RNA tumor viruses are controlled by a number of identifiable dominant and recessive genes. Meier's group has identified two allelic genes, one in which the dominant allele specifies group-specific antigen expression (gs+); the other, the allelic recessive gene specifying gs- or the switched off state. Similar V+ and V- alleles specify the production or non-production of viruses. Host genes controlling gs antigen proteins of avian RNA viruses were reported earlier by the British workers Payne, Chubb and Weiss.

Taylor and Meier have now derived recombinant inbred lines of mice from the mendelian crossing experiments using AKR (gs+,gs+) and C57L (gs-,gs-) having the following gs and V characteristics: (1) gs+,V+; (2) gs-,V-; (3) gs+,V-; (4) gs-,V+. Only line #1 has infectious virus. By crossing virus-negative lines 3 and 4, infectious virus is produced and released. This is best described as genetic rescue of the virus.

More recently Meier and Taylor have found that another strain of inbred mouse has a dominant gene specifying gs1: the F_1 cross AKR results in no gs expressions, and of course no virus expression. Thus by concentrating, in any strain or breed, genes for switching off gs antigen as has been done in the inbred mouse system, cancer could be virtually eliminated from such animals. While not directly applicable to the solution of human cancer, it provides enormously important concepts concerning the decisive nature of identifiable natural regulating genes in determining the incidence of cancer. This view was further supported by the results of F_1 backcross in the AK x L matings; the offspring at 20 months developed 102 tumors as follows: 91 tumors occurred in mice whose spleens were gs+ at birth. Nine of the 11 tumors from gs- mice (at birth) were gs+.

These data definitely suggest a linkage between the gs+ gene and the oncogene. The noninfectious gs expressions transmitted and controlled through succeeding generations can only be explained on the basis of genetic inheritance; thus infectious virus genomes have no need to be transmitted horizontally. These mendelian studies clearly establish the validity of the RNA viral oncogene theory so far as the inbred mouse is concerned.

II. B. Endogenous mechanisms. Molecular hybridization.

Molecular hybridization experiments employing the DNA products of avian and murine viruses and DNA of normal and tumor cells show that DNA copies of the virus produced by the reverse transcriptase sequences are present in normal as well as tumor cells, regardless of whether or not they have infectious virus. [Dr. Green, in HT-1(MSV) hamster cells; Duesberg, Bishop, Varmus and Levinson in avian cell systems; Scolnick, Aaronson and Parks in

virus-free mouse sarcoma cells]. We conclude from these findings that normal cells contain part or all of the sequences necessary to make RNA viruses.

III. A. Mechanisms of exogenous inducers of oncogenesis: RNA tumor viruses as determinants of transformation.

In vivo studies: In 1971 our associates (Whitmire, Salerno, Meier, Myers, Peters et al) and we have reported simultaneous activation of type C RNA tumor virus expressions (most often gs antigen, occasionally infectious virus) in chemically induced as well as spontaneous tumors in extensive surveys of many different inbred and outbred strains of mice. With the development in FY 1972 of the extremely sensitive radioimmune precipitation inhibition (RIPI) test developed by Parks and Scolnick, and Gilden and Oroszlan, many or most of the tumors which were gs negative by complement-fixation (CF) are now shown to be positive for gs antigen. We concluded from this that the coincident switch on of the major species-specific protein peptides of the RNA virus in tumor cells produced by a variety of chemical carcinogens (3MC, DMBA, BP and nitrosamines) provided evidence that the carcinogens act to derepress the RNA viral genome known to be present in mouse cells.

III. B. Evidence that activated "non-transforming" viruses carry oncogenic information. (Peters et al; Freeman, Price and Zimmerman et al)

Viruses activated and recovered from normal and tumorous mouse tissue, and from mouse cells (normal and transformed) grown in tissue culture were tested for oncogenicity in various ways. When injected into newborn mice of the isologous strain, up to 70% of the inocula have produced leukemia by 15 months; these experiments are still underway. Many such viruses are also being inoculated into genetically homologous and heterologous cell systems, following which they will be observed for many additional subcultures for evidence of spontaneous transformation (in comparison, of course, with controls); although extensive tests are still in progress, previous observations in various RNA virus-infected and uninfected mouse, rat and hamster cells revealed in most instances that spontaneous transformations occurred much earlier in infected cells; the onset of transformation often being determined by the genotype of the cells. We conclude from these observations and from numerous similar observations by others that wild type RNA viruses and their subinfectious virus expressions have oncogenic potential.

III. C. Activation of viral oncogenes in vitro.

Perhaps the most rapid and definitive test for oncogenic potential is one in which a given dose of RNA virus is added to mouse, rat and hamster cells together with small doses of carcinogenic chemicals (3MC, DMBA). As reported by Rhim, Freeman and Price, cells are readily transformed (from 9 days to 5 weeks) after adding both virus and chemicals; when only one is added, no transformation is observed, the cells behaving like untreated, uninfected cells. Recently it has been found that the dosage of input virus as well as titers of established virus present in the cells at the time of

treatment with 3MC were decisive determinants of transformation (Price and Zimmerman). If the virus level was less than 1.5 logs/ml of 10% cell pack extract, the cells generally were not transformed; higher virus titer levels apparently leads to increasing efficiency of transformation. Also, if the 3MC is added to the cells 24 hours before virus, transformation does not ensue. Recent experiments show that the presence of infectious virus does not increase permeability of the cells to the chemicals (Zimmerman).

We conclude from this that the added infectious RNA viruses provide large numbers of oncogenes available for derepression by the action of the carcinogenic chemicals.

IV. Rapid in vitro tests for environmental carcinogens based on prior infection of rodent cells with RNA tumor viruses.

Following up FY 1971 studies which indicated that rat and hamster cells infected with RNA tumor viruses provided extremely rapid sensitive and reproducible transformation assay systems for carcinogenic chemicals, Freeman and Price in FY 1972, working with Weisburger and others, tested fairly large numbers of non-carcinogenic analogs together with their related carcinogens in a standardized rat Rauscher leukemia virus-infected cell system. The positive and negative results obtained agreed remarkably well with the known in vivo carcinogenic activity of the chemicals tested. These and additional specimens are now on test in Dr. Rhim's virus-infected mouse and rat cell systems. In comparative tests, Rhim's Swiss mouse cell + AKR virus system was found to be the most sensitive of the various test systems, often yielding transformation endpoints within 2 to 3 weeks.

Effects of smog and tobacco smoke fractions: Freeman and Rhim separately tested (in their respective rat and mouse virus infected cell systems) several smog residues extracted in benzene and methanol and a number of fractions of tobacco smoke. All of the smog residues were profoundly oncogenic, showing 100 to 1,000 times more activity than the benzo(a)pyrene (BP) equivalents demonstrated in the smog preparations. Similarly, within relatively short intervals, Rhim found that 4 fractions of tobacco smoke were active as transforming agents in his mouse-AKR virus system. These fractions were among the 5 or 6 fractions furnishing significant numbers of epidermal tumors in mice as tested by Dr. Bock. The two strongest fractions in vivo were also the strongest transforming agents in Rhim's in vitro tests.

We conclude from these studies and previous studies not described here that Freeman's and Rhim's virus-infected in vitro test systems will have a definite and possibly a major role to play in identification and quantitative assays of chemical carcinogens in the environment.

V. Efforts to prevent endogenous RNA virus genome specified tumors.

In FY 1972 we embarked on serious attempts to search for agents that would have the best prospects for preventing or modifying cancer presumed from our other studies to be due primarily to endogenous but identifiable RNA virus gene products. We are studying natural cell repressors (Portugal and Simonds), interferon (Whitmire, Salerno), rifamycin derivatives (Green, Salerno, Rhim) as well as viral and cellular vaccines (Girardi and Whitmire).

All results are preliminary. However, Portugal and his associates have produced and fractionated cellular components from normal mouse cells carrying large amounts of Rauscher leukemia virus, which have shown moderate antiviral and antisarcoma effects on XC plaques and in vivo MSV tumor inductions. This promising lead will be followed up by tests against transformation in virus-free cells.

Salerno, Spahn and Whitmire have shown that high titered murine interferon given 3X a week completely prevented subcutaneous sarcomas normally inducible (at 80-90% level) by 3MC; the mouse used for this experiment was the outbred CF-1 strain which contains moderate amounts of overt RNA virus infection. The experiment is now being repeated using strains of mice that do not have viral expressions prior to tumor induction. We conclude from these results that the endogenous RNA virus genome was involved in the tumors induced by 3MC, since the action of interferon is strictly antiviral. Obviously interferons must be explored more intensively as anti-tumor agents.

A number of rifamycin derivatives having more activity against the RNA virus reverse transcriptase than against cell DNA polymerases have been identified by Drs. Green, Hackett and Calvin. Although moderately active against murine sarcoma viruses in vitro, the critical tests of these and future anti-polymerase products (as with interferon) will be in carcinogen-induced transformations and tumors in cells and animals in which overt virus is not normally expressed. Our associates have such systems and they will look for efficacy in them in cooperation with Green and Hackett.

We conclude that the evidence for efficacy of rifamycins or rifampicins in oncogenic test systems free of infectious virus is as yet non-existent; obviously until studies in such systems are proven positive, any claims for efficacy are exceedingly dubious.

Girardi has confirmed the finding by Coggins and his associates that "vaccine" preparations of embryonic hamster tissues have suppressive effects on hamster tumors; however both found effects only in male hamsters, suggesting effects other than specific immunogens. In a preliminary experiment, Whitmire and associates found that crude cell extract vaccines had a moderate suppressive effect on tumors induced by 3MC; additional experiments are in progress. Our present view is that anti-RNA tumor virus vaccines are unlikely to have much effect on natural or chemically induced cancers in natural situations (switched off for RNA virus expressions), at least where cancer develops

in the absence of overt RNA virus infections. However this assumption should not prevent relatively easily performed additional experiments.

VI. Immunological studies.

The influences of immunological surveillance mechanisms on cancer incidence in animal systems are well documented. This is particularly evident in the inbred mouse study systems where the effects of thymus removal and treatment with immunosuppressants (Imuran and anti-thymic or anti-lymphoid cell sera) leads to increased spontaneous cancers as well as those induced by viruses or chemicals (Meier and others). In chickens and in mice we and our associates have observed that high natural antibodies to the type C RNA virus greatly reduces natural virus expressions and cancer incidences.

Recent studies of the Hellstroms of cell mediated and humoral immunity against human cancers have been extremely productive. First of all they have shown that 80% of all cancer patients have detectable immunity against their own cancers and many to the same type of "organ-specific" tumors in other cancer patients. More recently they discovered that patients with growing cancers developed antibodies that block protective tumor cell cytotoxicity. When tumors were removed or otherwise responsive to therapy, they discovered another category of antibodies,"unblocking" antibodies that abrogated the blocking antibodies. Sjogren and his associates, working with the Hellstroms, demonstrated both blocking and de-blocking antibodies in sera of rats carrying tumors induced by polyoma virus. Studies of the effect of blocking and particularly de-blocking antibodies on tumors induced in vivo by carcinogenic chemicals represent an important next step. The importance of such observations for possible immunotherapy and for predicting outcomes of other types of therapy are obvious.

VII. The search for specific human RNA tumor viruses (types C and B).

After years of searching for type C RNA tumor viruses in leukemias and other tumors of man and some otherwise unconfirmed "sightings" of unidentified "particles", as of July 1971 no viable candidate human type C viruses were available for study.

During FY 1972, the isolation of two bona fide candidates for human type C viruses were reported by two different SVCP-supported contract groups.

The ESP virus: The type C virus in the ESP human cell line reported by Priori and her associates was found by various investigators in SVCP including 3 in the VCB-STS programs to have mouse specific gs antigens. Two other investigators found the antigenicity of RNA dependent DNA polymerase (RDP) to have the properties of the mouse RDP. Since the properties of ESP virus have not been shown to be much different from the host cell modified viruses (RLV, KiMSV) grown in many different human cells, the true origin of this virus remains in doubt.

The type C RD114 virus: This virus, which remains the best human specific candidate, originated in McAllister's RD human rhabdomyosarcoma cells after passage of this cell line by Drs. Gardner and Officer through a fetal cat. The virus observed in the RD114 cells was at first assumed to be FeLV of the cat; however, subsequent intensive studies by 6 different VCB and STS groups revealed that the virus had none of the species specific gs-1 properties of FeLV or for those of the mouse, rat, hamster, chicken, or viper type C viruses. Also, while the envelope antigens and polymerase antigens were entirely unique and distinct from that of other available viruses, the gs-3 antigen of RD114 was the same as that of the mammalian interspecies specific antigens. The RNA $\longrightarrow$ DNA polymerase of RD114 was shown by Parks and Scolnick to be related to those of the woolly monkey and gibbon ape, thus suggesting that there may be common antigens in addition to gs-3 shared by a "primate group" of viruses. Although the RD114 is the best available candidate for a human type C RNA virus, conclusive evidence is not yet available. It will be necessary to demonstrate gs and other species specific antigens in additional type C isolates from human tissues or alternatively in human tumor cells. Because overt expressions of the human type C virus can be expected from many experiences to be rare, studies of viral RNA $\longrightarrow$ DNA hybridization with known tumor cell RNA or DNA may be required.

Hybridization studies with cat virus DNA by Baluda and Roy-Burman show no significant homologies with RD114 virus. Studies by M. Green (St. Louis University) in hybridizations between RD114 DNA and RNA's of Hodgkin's cancer cells have suggested an exceptionally high degree of homology. Since these studies are preliminary they will require much confirmation before the human nature of the RD114 virus can be accepted.

Type B RNA tumor viruses and natural history studies in humans and in mice.

VCB and STS scientists Parks, Gilden, Gardner, Henderson, Roy-Burman, Rongey and Zeve are collaborating with Spiegelman and Schlom in studies of mammary tumor viruses (MTV) in both human and mouse milk specimens. All available new and old techniques are utilized including tests of milk for RDP, type B particles and group-specific antigens. The collaborative effort is focused on the human mammary tumor problem which is dependent on the USC cancer surveillance study program (Henderson and associates) for locating and supplying milk specimens from lactating women who are daughters of cancer patients. Task 2 is electron microscopic examination by Gardner, Rongey and Zeve for type B (or C) particles. Task 3 is processing of the fresh milk specimens for RDP tests by Roy-Burman and his associates. Task 4 involves the actual testing for RDP by Spiegelman and Schlom, Parks and Scolnick, and Roy-Burman.

VIII. Comprehensive field and laboratory studies of the etiology and epidemiology of human and animal cancers.

In FY 1971 the USC contract study program, now in a new building furnished by USC (20,000 sq. ft.), was expanded to include surveillance of all human cancers in Los Angeles County. This cooperative program now includes extensive participation by USC Departments of Pathology, Ecology, Statistics, Epidemiology, Immunology, Microbiology, and a large part of the clinical staff. The Children's Hospital clinical staff and Research Institute, the Los Angeles Medical Society, the Los Angeles Demography Human and Animal Health Departments are all cooperating to a remarkable extent. Currently the Cancer Surveillance Program (CSP) includes participation of 83 hospitals furnishing 70% of the 30,000 hospital beds in Los Angeles County and City. Within a few months all of the hospitals with 100 or more beds will be fully participating. The CSP is designed by the end of FY 1973 to furnish within 3 weeks after histological diagnosis necessary information on all of the 20,000 cancer cases estimated to occur in Los Angeles, thus providing a "now" registry of still living cancer patients, many of whom will be available for contemporary epidemiological and etiological studies.

Specific epidemiological studies of human cancer.

Breast cancer: The purpose of this study is to find out if daughters of mammary tumor cases (and controls) have type B virus particles in their milk, and thus to determine if the human, like mouse, transmits mammary tumor virus in mother's milk. The cancer surveillance program has already provided a list of 247 living mammary cancer patients under age 60, with permission by physicians and patients to interview 129 having already been received; refusal rates run only 10% thus far. To date 41 milk specimens from daughters of cancer patients have been collected. Specimens from controls (no history of mammary cancer) are also being collected. These will be tested blindly for RDP and B particles as described above (VII). The specimen collections are being supplemented by an epidemiological survey based on historical family tree analyses for evidence of predisposition to cancer in general.

Hodgkin's disease: The relation of this disease to the following factors are under study: (1) tonsillectomy and appendectomy; (2) EB virus; (3) RNA tumor viruses; (4) HLA antigen phenotype; and (5) case clustering (as in Albany). The cancer surveillance program provides the case and control patients for contemporary study.

Preliminary observations have delineated apparent clusters in heroin addicts; five cases attended one junior high school. Tests by the Henle's of 40 cases showed 11 with antibody titers to EB virus of 1 to 160 or greater; the significance of this observation can only be clarified by further studies.

Green's very recent evidence of high levels of homology between RD114 type C RNA $\rightarrow$ DNA with RNA from Hodgkin's cases provides an exciting new area for molecular studies of tumor cells of Hodgkin's cases and tumors from other types of malignant lymphoma.

Young genital tract cancer: The USC surveillance group (headed up by Dr. Henderson) in cooperation with George Linden of the California Tumor Registry confirmed previous reports of increased vaginal cancers in the 10-19-year-old group; however, they also found an increase in cancer of the testis. Histories in the Los Angeles vaginal cancer patients indicate *in utero* exposure to maternal treatment with stilbesterol. Very preliminary findings suggest that bladder cancer may also be increased by this previously common treatment for threatened abortion.

Composition of airborne particles (smog) in 4 Los Angeles locations: The carcinogenic activity of Los Angeles smog extracts (in benzene and methanol) reported by Freeman and Rhim (see IV above) provided the impetus to analyze and fractionate the differing smogs available in 4 different areas of Los Angeles County. Benzene fractionations from three areas, while quantitatively different, were similar in composition, reflecting almost exclusively automobile emissions. The local area included other emissions from chemical plants and oil refineries. In one of the 4 areas, metals (iron, nickel, cobalt) were elevated, presumably due to iron smelting. Recently derived methanol extract fractions which were shown to be oncogenic by Rhim and Freeman contained large amounts of ammonia nitrate and will be studied further. Drs. Gordon and Bryan who are in charge of the Los Angeles smog collection and analysis have established valuable cooperative arrangements with the local and state programs concerned with environmental pollution, including air quality.

Natural history of cancer and type C and B RNA viruses in wild mice: Underway since 1969, this study has now provided valuable information on the natural cancers and RNA cancer virus expressions in a natural species. As in most other natural species, most populations of wild (feral) mice were found to be relatively free of type C RNA tumor virus expression during early and middle life (up to 20 months). The onset of almost all cancer was delayed until after 24 months of age; peaks of tumor incidences occurred at 27-29 months and at 33-40 months. In 7,000 mice observed, only 61 spontaneous tumors were observed at death--23 lymphomas, 8 sarcomas, 26 adenomas of the lung; 5 miscellaneous. Type C particles were observed by electron microscopy in 5 of 7 lymphomas, 0 of 8 sarcomas. Despite hundreds of attempts, only one mouse from these populations yielded infectious RNA tumor virus; this virus had all the properties of the type C viruses of laboratory mice except that the envelope was distinct from the Gross-like virus found in laboratory mice. Recently a new isolated population of wild mice was discovered (Lake Casitas area): 80% reveal infectious type C virus. Type B virus has been seen in about one third of the mammary gland tissues examined; however, these mice were not used for breeding after trapping, which probably accounts for the lack of mammary cancers in the geriatric females.

Natural history studies of type C RNA virus in cats with lymphoma, other cancers and anemia: In cats with cancer and/or anemia, gs antigen and type C particles were found to be quite common.

	gs antigen		type C particles	
Lymphomas	23/32	72%	26/37	70%
Sarcomas	1/4	25%	2/16	13%
Carcinomas	0/25	0%	10/37	37%
Anemia	9/10	90%	12/15	80%
Normal	2/20	10%	1/12	8%

In studies by Dr. Raymond Gilden of Flow Laboratories and Mr. Horace Turner of VCB, sera from over 80 cats with spontaneous or virus-induced lymphoma or sarcoma were all negative for antibody to species-specific gs antigen in CF and RIPI tests, thus confirming previous studies suggesting that cats are immunologically tolerant for this antigen.

An epizootic study of solid tumors among chickens: During October, 1971 increased numbers of solid tumors (fibrosarcomas, hemangiomas, nephroblastomas) were observed in 8-week-old chickens being processed as fryers in a USDA inspected packing plant located in Los Angeles. Such tumors had been rare to absent prior to the outbreak which followed the institution of the use of Marek's disease vaccines at birth. However, since some unvaccinated birds held as controls also revealed fairly high incidences of solid tumors, the role of the vaccine was not clear. However, virtually all of the solid tumors tested were positive for gs antigen at high levels. Studies by Vogt and Weiss of USC (also supported by STS funds) resulted in the isolation of both avian RNA tumor viruses and herpes viruses. As expected from previous VCB studies, no sarcoma-inducing viruses were recovered from the sarcomas. Interestingly, tests of typical Marek's disease lesions showed nearly 100% to be positive for type C RNA gs antigens. These findings suggest that natural Marek's disease virus and the vaccine (attenuated live turkey Marek's-like herpes virus) may in some fashion increase the virogene and oncogene expressions of type C RNA virus, thus leading to the solid tumors characteristically produced by the avian RNA tumor viruses. This study will continue during the next fiscal year in cooperation with the Los Angeles chicken industry and the USDA inspection department.

Additional Important New Findings and Developments

Preparation of molecularly purified species-specific gs antigens: Drs. Oroszlan and Gilden have now prepared highly purified (electrofocused) species-specific gs antigens and antisera in guinea pigs for the RNA tumor viruses of the following species: mouse, cat, rat, hamster, human? (RD114), viper and chicken. They are each species-specific in gel diffusion, radioimmune precipitation inhibition, and complement-fixation. Gilden, Parks,

Riggs, Turner, Huebner and Henderson are using these reagents for monospecific antigens and antisera in extensive searches for additional expressions of these subinfectious but specific expressions of RNA tumor viruses in the natural species. Such surveys have led to discoveries of infectious RNA tumor viruses in wild (feral) mice, cats and chickens with spontaneous tumors. Similar surveys for specific virus expressions are now planned in numerous human and other primate cancers, using antisera to specific gs and envelopes of the RD114, woolly monkey and gibbon ape virus - the latter in cooperation with Drs. Bustad, Kawakami and others working on the STS-SVCP contract at the University of California, Davis.

Discovery of woolly monkey and gibbon ape viruses: Drs. Theilen and Kawakami and associates at the University of California, Davis, reported isolations of viruses having the characteristic properties of type C RNA viruses from a sarcoma of a woolly monkey (SSV) and from a lymphosarcoma of a gibbon ape (SLV). Since both of these viruses can be grown in significant amounts in a number of primate cell lines, it should be possible soon to produce virus-specific gs and other viral antigens and antisera which should prove invaluable for doing natural history studies of virus and cancer incidences in these two species. Similarly, the species-specific and interspecies reagents should make it possible to determine possible cross reactions amongst the primate viruses. Of course the demonstration of type C RNA viruses in two primates increases the likelihood that the virus genome will also be found in humans.

Activation of EBV virus in virus-free Burkitt tumor (Raji) cells: Dr. Berge Hampar (VCB) and his associates reported activation of EBV virus in the EBV-free Raji strain of Burkitt's lymphoma with the use of BrdU, a finding confirmed by Dr. Paul Gerber of DBS. Using the same technique, Hampar also activated EBV virus in the Levene lymphoblastic cells recovered from pleural fluid. This procedure should make it possible to screen large numbers of lymphoblastic leukemia cell cultures for covert EBV virus. It may also help determine whether all virus-free Burkitt cell clones contain the genome.

Activation of type C RNA tumor virus expressions in cells transformed by polyoma virus: One of the major unanswered questions in viral transformation by the "oncogenic" DNA tumor viruses (polyoma, SV40, adenoviruses, and herpes type viruses) is the source of the transforming oncogene. Are the oncogenic genes responsible for cell transformation by the DNA viruses part of the viral DNA or the cell DNA; and further, does the endogenous RNA tumor virus genome participate in the transformation process?. Recent findings by Drs. Freeman, Kelloff, Rhim, Huebner, and Mr. Lane indicate that like chemical carcinogens (see III above), polyoma and SV40 viruses do interact with RNA tumor virus genomes. Tumors and transformed cells in NIH Swiss mice and in hamsters induced by polyoma virus reveal large amounts of species-specific gs antigen when the cells are transplanted subcutaneously in newborns of these respective species. The local hamster tumors have infectious HaLV as well as gs antigen; neighboring and other tissues (spleen, thymus, etc.) are negative for antigen and virus. When polyoma-transformed NIH Swiss

cells were transplanted into newborn Swiss mice the tumors were strongly positive for gs antigen but negative for infectious virus. Since the normal hamster and NIH Swiss mouse otherwise are negative for infectious viruses, and the latter apparently cannot under any conditions make infectious virus (Rowe, Hartley and Huebner), the evidence favors amplification in the tumor of RNA virus expressions induced by the polyoma virus. Since polyoma, SV40 and adenoviruses have not been shown to cause tumors in their natural hosts (extensive data are universally negative) we interpret these findings as favoring the hypothesis that neoplastic changes produced in heterologous cells and animals by these viruses are due to derepression or activation of the RNA virus genome.

Temperature sensitive mutants of avian sarcoma and polyoma viruses: Conditional lethal (ts) mutants of tumor viruses represent one of the tools for measuring the specific activities of viral genes in virus replication and neoplastic transformation or tumor induction. Walter Eckhart of the Salk Institute, in producing a number of genetically stable mutants of polyoma virus, has been able to show the importance of polyoma viral gene determinants in maintaining the transformed state and also for T antigen expressions. Similarly, Peter Vogt and his associates at USC have established a number of mutants of Rous sarcoma virus. With Dr. Max Burger he has shown that when a Rous virus mutant was shifted from permissive to the nonpermissive temperature, the cells lost much of their agglutinability with jack bean agglutinins. When returned to permissive temperatures, the agglutinability returned to previous levels.

Recapitulation:

The first order of business we believe is to identify the nature and the origins of the cancer-inducing oncogenes in cells. During the past two years SVCP-supported and other scientists have gone a long way towards achieving this first objective, having demonstrated the validity of the RNA viral oncogene hypothesis (and perhaps to some extent the Temin protovirus hypothesis) in at least 4 distinct categories of vertebrate animals (mouse, rat, hamster and chicken). Other associates working with inbred mice and chickens have succeeded, with mendelian crossing and backcrossing experiments, in identifying host genes which regulate and therefore serve as determinants of expression of the inherited virogenes and oncogenes which make up the RNA tumor virus genome. Additional new information relates to inborn genetic defects of inbred animals which are known to predispose and predetermine high risks of many types of cancer; cancers quite similar to those which in man are also attributed to genetic defects.

It is a matter of record that the VCB-STS programs have assumed leadership in developing the technological tools needed for identification and quantitation and assays of natural and induced expressions of the genes of the RNA tumor viruses in normal and neoplastic cells.

We have also developed new very sensitive and rapid in vitro test systems for quantitative assay of carcinogenic chemicals found in increasing amounts

in human environments. In these tests we are measuring simultaneously in the several cell systems the carcinogenic transforming effects in cell cultures of (a) endogenous viral genomes and (b) added virus genomes and of the exogenous chemicals.

We are employing newly developed simplified but sensitive serological procedures in large scale natural history studies of natural expressions of RNA tumor viruses in human, feral mouse, cat, rat and chicken populations in natural ecologies with the purpose of determining the role of these virus expressions in the spontaneous cancers of these species.

Several projects in STS and VCB are engaged in (1) studies in cell cultures and inbred animals of natural and synthetic oncogene (and virogene) suppressing chemicals, and (2) studies of natural and induced immune responses that offer hope for immunological control of cancer.

Obviously, therefore, there is no way to avoid emphasizing the fact that the main focus of the VCB and STS research program is the study of the validity of the RNA viral oncogene hypothesis proposed by VCB scientists in 1969. The hypothesis agrees with most geneticists working in cancer that the genetic determinants (seeds) of the cancerous changes in a cell are part of natural gene inheritance; therefore these gene determinants (according to modern understanding of the genetic code) must be represented on the cellular DNA as polynucleotide sequences of all vertebrate cells. The hypothesis, however, further proposes that the information in all vertebrate cells has the capacity to make most or all of components (RNA $\rightarrow$ DNA and proteins) of the RNA tumor viruses, including the transcriptase and translation products required for oncogenic transformation. Of course, like many other cell genes, it is postulated that the RNA virus genome is properly controlled by host regulating gene systems in order to insure species survival. It is presumed that in an evolutionary context, infectious RNA (tumor) viruses must have provided certain advantages at one time in pre-vertebrate periods, but that now infectious expression and horizontal transmission (although occasionally observed) is no longer necessary for survival of the genome. This implies of course that horizontal transmissions of the RNA tumor virus genome in most higher species as a direct cause of cancer is likely to be rare or non-existent.

In higher vertebrates - in dogs, other domestic animals, primates and humans - where overt virus expression is rarely observed occurring spontaneously, expression of either the virogene or oncogene is viewed as the consequences of (a) genetic defects detected early in life, or (b) breakdowns of gene regulation and immune surveillance later in life due to environmental, mutagenic and/or oncogenic factors, or in many cases, simply senescence.

Finally, it is clear that the oncogene hypothesis and the concept of universal inheritance of the RNA tumor virus genome was not the result of brilliant intuition, but an inescapable conclusion forced on us by the overwhelming weight of extensive data, some of it old, but much of it contemporary, which revealed that the phenotypic expressions (often noninfectious) of the virus

in association with neoplastic state did not depend in nature on horizontal spread of infectious virus despite an occasional overt manifestation. When it was found that expressions of group-specific (gs) antigen expressions of the virus were commonly expressed in spontaneous and induced tumors and embryonic tissues of inbred mice, chickens and hamsters, most often in the total absence of infectious virus, it could only be concluded that the genome must be inherited.

C. CONTRACT PROGRAM

1. RESEARCH LOGIC

FOR

SPECIAL VIRUS CANCER PROGRAM

VIRAL ONCOLOGY - NCI

AUGUST 1972

See Fold-In Chart inside back cover to be used in conjunction with Table III, pages 108 through 122.

C. CONTRACT PROGRAM

2. Major Program Modifications of Viral Oncology Contracts:

Flexibility within a program is necessary if effective program management is to provide responsiveness to changing program needs. This requires constant monitoring and evaluation of each scientific project in terms of need, priority and relevance to specific program objectives within the framework of available funds. This task is time consuming and requires constant attention because of the number of contracts to be monitored, the complexity of many of the contracts, and the necessity for reappraisal of their scientific objectives as priorities, degrees of relevance, and need, change in the light of accomplishments, failures, and newer information.

One early accomplishment of the planning team of the Special Virus Cancer Program was the recognition of this need for flexibility so that the program would be responsive to changing requirements. Indeed, it is program management of this type which in part separates the contract support mechanism from the grant support mechanism.

This report is a summary documentation of major modifications of contracts within the Viral Oncology Area for the period ending June 30, 1972. The actions include (1) termination, (2) modification of workscope, (3) change of emphasis within existing workscope, and (4) initiation of new contracts.

SUMMARY: MAJOR MODIFICATION OF VIRAL ONCOLOGY CONTRACTS

July 1, 1971 - June 30, 1972 *

ACTION	PREDOMINANT REASONS	NO. OF CONTRACT MODIFICATIONS
Termination	Work Successfully completed	5
Termination	Consolidate work and/or contracts	5
Termination	No longer high priority	9
Modification of existing workscope	Decrease activity of low priority with re-direction	4
Modification of existing workscope	Expansion of activity of high priority	7
Modification of existing workscope	Initial work successfully completed New work of high priority initiated	3
Change of emphasis with workscope	To exploit new information, to respond to changing program priorities, to provide maximum program flexibility	3
New contract	Satisfy program needs	31
TOTAL NUMBER OF CONTRACT MODIFICATIONS		67

*Refer to previous similar documents for a complete testing and analysis of major modifications for all Viral Oncology contracts within the SVCP since FY '65.

C. CONTRACT PROGRAM

3. TABLE I ANALYSIS OF CONTRACTS BY SEGMENTS
(By Type of Institution)
Viral Oncology, DCCP, NCI

Segment	Profit		Educational		Non-Profit		Other*		Total	
	No.	Amount**	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Program Management	3	2,157	5	338	0	0	2	1,035	10	$3,530
Developmental Research	3	2,588	10	4,386	8	1,114	0	0	22	8,088
Solid Tumor Virus	6	6,390	10	5,210	3	585	1	35	20	12,220
Immunology	2	257	8	883	4	346	2	906	16	2,392
Resources and Logistics	16	7,241	12	1,810	7	587	1	37	35	9,675
Breast Cancer Virus Studies	2	562	5	508	4	654	0	0	11	1,724
Biohazards and Environ. Cont.	1	200	2	388	0	0	1	67	4	655
Tumor Virus Detection Segment	1	792	9	1,240	2	122	1	650	13	2,804
TOTAL	34	20,187	61	14,763	28	3,408	8	2,730	131	41,088

* Included interagency agreements
** Dollars in Thousands

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 1: SELECTION OF VIRUS SOURCES

Contractor	Cont. No.	Description of Work
Aichi Cancer Center	69-96	Seroepidemiological studies of BL, NPC in Southeast Asia
Baylor University	68-678	Seroepidemiology of cervical carcinoma
California SDPH	69-87	Human-feline retrospective epidemiological studies
California, Univ. of	72-2008	Serological studies on the relationship of HL-A type to cancer incidence
CDC	VCL-42	Epidemiological studies of selected leukemia cases (clusters)
Children's Hosp. (Phila)	66-477	Immunological studies of EBV-associated cancers
Georgetown University	65-53	Collaborative studies on populations at high risk to breast cancer
IARC	70-2076	Seroepidemiological study of BL and NPC in Southeast Asia and Africa
Inst. for Med. Res.	68-1000	Collaborative studies on populations at high risk to breast cancer
Jewish Hospital	72-2034	Genetic analysis of human cancer associated with chromosomal abnormalities
Johns Hopkins Univ.	71-2121	Seroepidemiology of cervical carcinoma
Karolinska Institute	69-2005	Immunological studies of EBV-associated cancers
Makerere University	67-47	Epidemiological studies of Burkitt Lymphoma in Uganda
Michigan Cancer Fdn.	71-2421	Collaborative studies on populations at high risk to breast cancer
Minnesota, Univ. of	71-2261	Immunological studies of high risk groups with immunodeficiency diseases

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 1: SELECTION OF VIRUS SOURCES (continued)

Contractor	Cont. No.	Description of Work
Southern Calif., Univ. of	68-1030	Cancer surveillance and epidemiologic studies in Los Angeles County
Texas, University of	65-604	Serological studies of human leukemia, lymphoma, and solid tumors
Texas, University of	71-2135	Gather information on laboratory-acquired infections
Wolf R & D	71-2270	Develop computerized system for collection and storage of clinical and epidemiological information

TABLE II Analysis of Contracts by Activity

PHASE I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 2: SOURCES OF VIRUS OR SUBVIRAL MATERIAL

Contractor	Cont. No.	Description of Work
Aichi Cancer Center	69-96	Acquire normal fetal and tumor tissue
Auerbach Associates	72-2023	Develop integrated systems for collection, storage, and distribution of resources.
Baylor University	68-678	Acquire clinical data and specimens of human neoplastic tissues
California, Univ. of	72-2008	Acquire clinical data and specimens of normal and neoplastic tissue
CDC	VCL-42	Collection of clinical data and specimens from human leukemias
Colorado University	69-2080	Pediatric and adult tumor specimens
Georgetown University	65-53	Acquire clinical data and human breast cancer specimens
Hospital for Sick Child.	65-97	Human leukemia and normal tissue collection
Howard University	70-2178	Acquire clinical data and human breast cancer specimens
IARC	70-2076	Acquire clinical data and specimens from BL and NPC.
Jewish Hospital	72-2034	Supply normal and neoplastic tissues from patients with various chromosomal abnormalities
Johns Hopkins Univ.	71-2109	Acquire clinical data and specimens from human leukemias and lymphomas
Karolinska Institute	69-2005	Acquire clinical data and specimens from BL, NPC, and leukemias
Makerere University	67-47	Collection of Burkitt Lymphoma specimens
Memorial Hospital (N.Y.)	71-2116	Acquire clinical data and specimens of human neoplastic tissue

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 2: SOURCES OF VIRUS OR SUBVIRAL MATERIAL

Contractor	Cont. No.	Description of Work
Memorial Hospital (N.Y.)	71-2194	Supply clinical data and specimens for human breast cancer studies
Michigan Cancer Fdn.	71-2421	Acquire clinical data and specimens for human breast cancer studies
Michigan, Univ. of	65-639	Collection of adult leukemia/lymphoma specimens
Minnesota, Univ. of	71-2261	Acquire clinical data and specimens from patients with immunological deficiency diseases
Montreal Children's Hosp.	65-1020	Collection of human leukemia and normal blood specimens and normal tissue
Padua, University of	68-1389	Collection of untreated human tumor and normal tissue specimens
Southern Calif., Univ. of	68-1030	Acquire clinical data and specimens of human neoplastic tissues
St. Joseph's Hospital	69-2074	Acquire clinical data and human sarcoma and breast cancer specimens
Texas, Univ. of	65-604	Acquire clinical data and specimens of human neoplastic tissue

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 3: DETECTION OF VIRUS OR VIRUS EXPRESSION

Contractor	Cont. No.	Description of Work
Aichi Cancer Center	69-96	Detection using cell culture techniques-human tumors
Atomic Energy Commission	FS-7	Developmental research on immunological detection of tumor antigens--fetal antigens
Atomic Energy Commission	FS-13	Detection using immunological techniques
Baylor University	68-678	Detection using immunological and cell culture techniques
California, Univ. of (Davis)	70-2048	EM, biochemical, immunological techniques in comparative leukemia/sarcoma virus studies
California SDPH	68-997	Studies on the role of oncogenic viruses in cancer of man and domestic animals
California, Univ. of	72-2008	Detection using immunological techniques
California, Univ. of (also NBL, FS-8)	63-13	Tissue culture studies of normal and neoplastic human tissues
Children's Hospital (Phila)	66-477	Immunological detection of EBV-associated antigens in human cancer
Columbia University	70-2049	Screening human leukemia/lymphoma specimens with biochemical techniques
Cornell University	71-2508	Isolation, characterization of cat leukemia viruses
Cornell University	70-2224	Service - feline virus diagnostic laboratory
Einstein Medical College	65-612	Genetic studies on tumor/virus susceptibility
Flow Laboratory	71-2097	Immunological studies of mammalian Type C viruses
Georgetown University	65-53	Human breast cancer detection - biochemical techniques

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 3: DETECTION OF VIRUS OR VIRUS EXPRESSION (continued)

Contractor	Cont. No.	Description of Work
Harvard University	72-3246	Virus detection in non-human primates
Hazleton Labs	69-2079	Immunological/biochemical detection of virus in animal/human tumors
Howard University	70-2178	Immunological studies of human breast cancer
Huntingdon Research Ctr.	69-54	Immunological reagent production
IARC	70-2076	Immunological studies of BL, NPC
Indiana University	69-2048	Immunological characterization of avian RE tumor virus
Institute for Med. Res.	68-1000	Screening human and animal breast cancer specimens by EM, immunological techniques
Jackson Labs	67-744	Genetics of susceptibility to cancer in mice
Johns Hopkins University	71-2121	Immunological studies on Herpesvirus antigens in cervical carcinoma
Johns Hopkins University	71-2109	Immunological studies of human leukemia and lymphoma
Karolinska Institute	69-2005	Immunological studies of EBV-associated human neoplasia
Litton-Bionetics	71-2025	Screening of human/primate neoplastic tissue with biochemical techniques
Litton-Bionetics	69-2160	Detection using immunological techniques
Mason Research Institute	70-2204	Development of primate test systems for breast cancer virus detection
Meloy Labs	72-3202	Immunological studies of murine mammary tumor virus

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 3: DETECTION OF VIRUS OR VIRUS EXPRESSION (continued)

Contractor	Cont. No.	Description of Work
Meloy Labs	72-2006	Detection using immunological, biochemical and tissue culture techniques
Michigan Cancer Fdn.	71-2421	Virus detection in human breast cancer by biochemical techniques
Microbiological Assoc.	70-2068	Detection using immunological and cell culture techniques
Microbiological Assoc.	67-697	Bioassay of murine leukemia/sarcoma viruses
Microbiological Assoc.	67-700	Service - murine viral diagnostic reagents and testing
Minnesota, Univ. of	69-2061	Development of immunological tests for tumor antigens and antibodies
Minnesota, Univ. of	71-2261	Immunological and virological studies of immunodeficiency diseases
Netherlands Cancer Inst.	72-3260	Immunological detection of natural MTV expression
Ohio State University	65-1001	Immunological testing (PRILAT) for human tumor antigens and antibodies
Ohio State University	69-2233	See OSU 65-1001
Pennsylvania, Univ. of	65-1013	Studies of viruses associated with bovine leukemia
Pennsylvania State	70-2024	Biochemical, genetic studies of Herpes-type viruses
Pfizer, Chas., and Co.	67-1176	Detection of virus by EM-human and animal breast cancer
Princeton University	71-2372	Detection of cell membrane antigens by agglutination techniques
Public Health Res. Inst.	71-2129	Development of methods for isolation of virus from human neoplasia

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 3: DETECTION OF VIRUS OR VIRUS EXPRESSION (continued)

Contractor	Cont. No.	Description of Work
Robert Brigham Hosp.	71-2172	Detection using immunological methods
Rush-Presbyterian	71-2032	Immunological, biological, tissue culture studies of tumor viruses in non-human primates
Salk Institute	67-1147	Genetic, biochemical studies of viral-induced transformation
Salk Institute	72-3207	Immunological detection of tumor antigens
Scripps Clinic	72-3264	Development of new immunological technologies for detection of virus expression
Southern Calif., Univ. of	68-1030	Immunological studies of human fetal and tumor tissues
Stanford University	69-2053	Development of cell culture methods for human tissue
St. Joseph's Hospital	69-2074	Screening of human sarcomas by EM
St. Louis University	67-692	Detection using tissue culture and biochemical techniques
Tel Aviv University	72-3237	Biochemical detection of tumor viruses in human breast cancer
Texas, Univ. of	65-604	EM, tissue culture and immunological studies of human neoplastic tissues
Texas, Univ. of	71-2178	Immunological methods for detection of human tumor antigens and antibodies
Washington, Univ. of	71-2171	Development of immunological tests for tumor antigens and antibodies
Weizmann Institute	69-2014	Detection of tumor cell surface antigens by plant agglutinins

TABLE II Analysis of Contracts by Activity

Phase I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
Step 3: DETECTION OF VIRUS OR VIRUS EXPRESSION (continued)

Contractor	Cont. No.	Description of Work
Wisconsin, Univ. of	72-2022	Techniques for isolation and characterization of viral-induced tumor antigens
Wistar Institute	71-2092	Techniques for isolation and characterization of viral-induced tumor antigens

TABLE II Analysis of Contracts by Activity

Phase II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
Step 1: ESTABLISH REPLICATION OF VIRUSES

Contractor	Cont. No.	Description of Work
Baylor University	68-678	Human leukemia transmission studies in non-human primates
Biolabs, Inc.	72-2068	Development and improvement of *in vitro* production of Herpes-type viruses
California SDPH	68-997	Isolation and characterization of feline tumor viruses
California, Univ. of	63-13	Development and evaluation of cell cultures for viral oncology research
California, Univ. of	70-2048	*In vitro* and *in vivo* studies of simian and feline virus infectivity and replication
California, Univ. of	72-2080	Development of methods for *in vitro* propagation of MTV
Children's Hosp. (Phila)	66-477	Developmental research on growth and replication of EBV in human cell lines
Cornell University	71-2508	Isolation and characterization of feline tumor viruses
Duke University	71-2132	Production and characterization of avian leukosis viruses
Electronucleonics	71-2253	Production and characterization of selected mammalian oncogenic viruses
Emory University	72-2301	Production of Herpes-type viruses
Flow Labs, Inc.	71-2097	Large-scale production of RNA tumor viruses for production of highly-specific diagnostic reagents
Harvard University	72-3246	Determination of host-range of primate oncogenic viruses
Hazleton Labs	69-2079	Isolation and production of ts-mutants of RNA tumor viruses
IARC	70-2076	Growth and replication of Herpes-type virus in nasopharyngeal carcinoma and Burkitt's lymphoma specimens

TABLE II Analysis of Contracts by Activity

Phase II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
Step 1: ESTABLISH REPLICATION OF VIRUSES (continued)

Contractor	Cont. No.	Description of Work
Karolinska Institute	69-2005	Growth and replication of Herpes-type viruses
Life Sciences	69-63	Production and infectivity studies of Marek's disease virus
Litton-Bionetics	71-2025	Inoculation of nonhuman primates with various animal virus and human materials
Mason Research Inst.	70-2204	Studies on infectivity and effect of hormones on monkey mammary tumor virus replication
Medical Coll. of Wisconsin	68-1010	Stimulation of Type C virus production in human breast cancer cell line by various hormones
Meloy Labs	72-3202	In vitro and in vivo production of murine mammary tumor virus
Meloy Labs	72-2006	Growth and replication of mammalian Type C and syncytial viruses for tissue culture; biochemical studies of mammalian and avian tumor viruses
Miami University	70-2211	In vitro production of rat mammary tumor derived virus
Microbiological Assoc.	67-697	Cell-free transmission of murine mammary tumors with extracts from spontaneous tumors
Microbiological Assoc.	70-2068	Isolation, characterization, and transmission studies of mammalian and avian tumor viruses
Naval Biological Lab	FS-57	Studies of environmental factors influencing virus-host interactions--research on laboratory biohazards
North Dakota Univ.	66-8	Role of vectors in transmission, host range of tumor viruses
Ohio State Univ.	65-1001	Studies on factors affecting horizontal transmission of tumor viruses
Pennsylvania State	70-2024	Herpes-type virus replication in human cells

TABLE II Analysis of Contracts by Activity

Phase II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
Step 1: ESTABLISH REPLICATION OF VIRUSES (continued)

Contractor	Cont. No.	Description of Work
Pennsylvania, Univ. of	65-1013	Experimental and natural transmission of bovine leukemia
Pfizer, Chas. & Co.	70-2080	Tissue culture production of Type C and Herpes-type viruses
Pfizer, Chas. & Co.	67-1176	Production of monkey and rat suspected oncogenic viruses
Rush-Presbyterian	71-2032	Mammalian tumor virus infectivity in nonhuman primates
Southern Calif., Univ. of	68-1030	Production of mammalian RNA tumor virus and candidate human agents
Southwest Foundation	71-2348	Study of latent virus infection and transmission--research on laboratory biohazards
St. Jude's Hospital	71-2134	Isolation and characterization of oncogenic Herpes-type viruses
St. Louis University	67-692	In vitro cultivation of various mammalian Type C tumor viruses for biochemical studies
Texas, University of	65-604	Infectivity, oncogenicity and host range studies of hamster sarcoma virus; isolation and characterization of candidate human Type C oncogenic virus
University Labs	66-1133	In vitro and in vivo production of murine and avian tumor viruses

TABLE II Analysis of Contracts by Activity

Phase II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
Step 2: INITIAL CHARACTERIZATION

Contractor	Cont. No.	Description of Work
Baylor University	68-678	Comparative characterization of human Herpes-type viruses
California, Univ. (Davis)	70-2048	Comparative studies on simian leukemia/sarcoma viruses
Children's Hospital (Phila)	66-477	Immunological, tissue culture characterization of EBV
Columbia University	70-2049	Biochemical characterization of mammalian Type C viruses
Cornell University	71-2508	Immunological characterization of feline tumor virus isolates
Duke University	71-2132	Immunological characterization of RNA tumor viruses
Emory University	72-2301	Serological studies on Herpes-type virus antigens
Flow Labs	71-2097	Immunological, tissue culture studies of mammalian DNA and RNA oncogenic viruses
Harvard University	72-3246	Characterization of simian oncogenic Herpes-type viruses
Hazleton Labs	69-2079	Characterization of ts mutants of RNA tumor viruses
IARC	70-2076	Isolation and characterization of Herpes-type virus in cultures of Burkitt's lymphoma and nasopharyngeal carcinoma
Indiana University	69-2048	Immunological, biochemical characterization of avian RE virus
Karolinska Institute	69-2005	Immunological and biochemical characterization of EBV
Life Sciences	69-63	In vitro and in vivo studies of Marek's disease virus
Meloy Labs	72-2006	Biochemical characterization of mammalian Type C viruses

TABLE II Analysis of Contracts by Activity

Phase II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
Step 2: INITIAL CHARACTERIZATION (continued)

Contractor	Cont. No.	Description of Work
Meloy Labs	72-3202	Immunological characterization of murine MTV
Miami University	70-2211	EM, biological, biochemical characterization of rat mammary tumor derived virus
Microbiological Assoc.	70-2068	Immunological characterization of mammalian Type C tumor viruses
Pennsylvania State	70-2024	Genetic, biochemical studies of cells "transformed" by viral (Herpes-simplex)--chemical cocarcinogenesis
Pennsylvania, Univ. of	65-1013	Characterization of Type C virus associated with bovine leukemia
Rush-Presbyterian	71-2032	Immunological, biological characterization of Herpes viruses of nonhuman primates
Scripps Clinic & Res. Fdn.	72-3264	Development and improvement of specific viral diagnostic reagents
Southern Cal., Univ. of	68-1030	Immunological characterization of mammalian tumor viruses
St. Jude Children's Res. Hosp.	71-2134	Characterization of suspected oncogenic Herpes-type viruses
St. Louis University	67-692	Biochemical characterization of oncogenic RNA and DNA viruses
Texas, Univ. of	65-604	Studies on the relationship of animal tumor viruses to human leukemia and lymphomas; characterization of candidate human Type C oncogenic virus
TRW	70-2200	Improvement of methods for production of specific viral diagnostic reagents
Wisconsin, Univ. of	72-2022	Isolation and characterization of subunits of RNA tumor viruses
Wistar Institute	71-2092	Isolation and characterization of oncogenic DNA and RNA virus-induced tumor antigens

TABLE II Analysis of Contracts by Activity

Phase II-B: REPLICATION AND CHARACTERIZATION OF VIRUS EXPRESSION
Step 1: INDUCE VIRAL REPLICATION OF WHOLE VIRUS OR TRANSMISSION OF EXPRESSION

Contractor	Cont. No.	Description of Work
Aichi Cancer Center	69-96	Tissue culture methods to induce virus replication in human tumor cells
AEC	FS-13	Induction of virus expression by cell fusion techniques
Baylor University	72-2058	Development of "nonsense" suppressor mutant cell lines for viral genome characterization
California SDPH	68-997	Establish cultures from tumors of domestic animals and attempt to rescue defective viral genome
California, Univ. of	63-13	Tissue culture of human neoplastic tissue for induction of virus replication
Flow Labs	71-2097	Cell hybridization techniques to rescue "defective" viruses
Hazleton Laboratories	69-2079	Transmission of oncogenic virus expression in selected cell systems
Hôpital St. Louis	72-3263	Induction and transmission of oncogenic virus expression in human cells
Illinois, Univ. of	72-2031	Development of methods for recognition of virus expression
Medical Coll. of Wisc.	68-1010	Co-cultivation of human breast cancer and hormone-secreting cell lines
Meloy Labs	72-2006	Characterization of non-producer transformed cells; virus rescue techniques
Microbiological Assoc.	67-697	Effect of hormones on virus expression
Microbiological Assoc.	70-2068	Studies on Type C viral genome expression--effect of chemical carcinogens
Pennsylvania State	70-2024	Induction and maintenance of human Herpes-type virus oncogenicity
Public Health Res.	71-2129	Rescue of viruses from human tumors

TABLE II Analysis of Contracts by Activity

Phase II-B: REPLICATION AND CHARACTERIZATION OF VIRUS EXPRESSION
Step 1: INDUCE VIRAL REPLICATION OF WHOLE VIRUS OR TRANSMISSION OF EXPRESSION (continued)

Contractor	Cont. No.	Description of Work
Salk Institute	67-1147	Studies on the activation of Type C virus genome by polyoma virus
Southern Cal., Univ. of	68-1030	Studies of virus expression in human fetal and tumor tissue
Southern Cal., Univ. of	72-2032	Methods for recognition and/or rescue of tumor virus expression
Stanford University	69-2053	Tissue culture, biochemical methods to induce virus replication in human tumor cells
Tel Aviv University	72-3237	Development of methods for recognition of virus expression in human breast cancer
Texas, Univ. of	65-604	Attempts to induce viral replication in human cell lines

TABLE II Analysis of Contracts by Activity

Phase II-B: REPLICATION AND CHARACTERIZATION OF VIRUS EXPRESSION
Step 2: INITIAL CHARACTERIZATION

Contractor	Cont. No.	Description of Work
Atomic Energy Commission	FS-13	Biochemical studies on regulation of gene expression
California, Univ. of	71-2147	Molecular studies of avian tumor-virus-associated enzymes
California, Univ. of	71-2173	Molecular studies of the structure of oncogenic viruses and characterization of viral-specific enzymes
California, Univ. of	72-3236	Characterization of growth regulatory mechanism in normal and neoplastic cells
Columbia University	70-2049	Biochemical characterization of viral-specific enzymes
Einstein College of Med.	71-2251	Biochemical characterization of viral-specific enzymes and other proteins
Flow Labs	71-2097	Characterization of tumor virus expression in mammalian systems
Hazleton Laboratories	69-2079	Characterization of cellular and subcellular alterations in viral transformation
Massachusetts Gen. Hos.	71-2174	Characterization of nucleic acids and proteins of AMV
Mass. Inst. of Technol.	71-2149	Biochemical characterization of viral-specific enzymes
Meloy Labs	72-2006	Multidisciplinary approaches to characterization of virus-expression and mediators of replication
Microbiological Assoc.	70-2068	Immunological identification of antigens related to known tumor viruses
North Carolina, Univ. of	72-3228	Biochemical identification of DNA viral genome in human cells
Oregon State Univ.	71-2175	Correlation of ultrastructural and biochemical changes associated with transformation by viruses
Princeton Univ.	71-2372	Characterization of cell membrane changes in malignant transformation

TABLE II Analysis of Contracts by Activity

Phase II-B: REPLICATION AND CHARACTERIZATION OF VIRUS EXPRESSION
Step 2: INITIAL CHARACTERIZATION (continued)

Contractor	Cont. No.	Description of Work
Public Health Res.	71-2129	Identification of cellular and subcellular alterations characteristic of malignant transformation
Public Health Res.	72-2028	Characterization of cell membrane changes in malignant transformation
Scripps Clinic & Res. Fdn.	72-3264	Development and improvement of immunochemical methods for the detection of cell membrane changes induced by oncogenic viruses
Southern Calif., Univ. of	68-1030	Immunological identification of antigens related to known tumor viruses
Southern Calif., Univ. of	72-2032	Establishment of methods for identification of virus-induced transformation
St. Louis Univ.	67-692	Multidisciplinary approaches to characterization of oncogenic virus expression and mediators of replication
Tel Aviv Univ.	72-3237	Biochemical identification of subviral expression in breast cancer
Texas, Univ. of	65-604	Characterization of in vitro transformation of human sarcoma cells
Weizmann Institute	69-2014	Improvement of immunochemical methods for detection of cell membrane changes in viral transformation
Wisconsin, Univ. of	72-2022	Development of immunochemical reagents and tests for detection of virus expression in chemically-induced tumors

TABLE II Analysis of Contracts by Activity

Phase III-A: COMPLETE CHARACTERIZATION AND DEFINITION OF PRESUMPTIVE DISEASE RELATIONSHIPS
Step 1: PRESUMPTIVE DISEASE RELATIONSHIPS

Contractor	Cont. No.	Description of Work
Atomic Energy Comm.	FS-13	Interaction of RNA tumor viruses and host immune mechanism; studies on relationship of embryogenesis and carcinogenesis
Baylor University	68-678	Studies on presumptive disease relationships of HTV
California SDPH	68-997	Serological testing of host reactions to tumor virus antigens
Children's Hosp. (D.C.)	72-2071	Cell-mediated immunity to human cancers
Children's Hosp. (Phila.)	66-477	Relationship of EBV to human lymphoma
Columbia University	70-2049	Biochemical studies on relationship of Type C and Type B viruses to human leukemia/sarcoma and breast cancer
Einstein Medical College	65-612	Genetic studies on tumor/virus susceptibility
Emory University	72-2301	Determination of host response to Herpes-type virus in cervical cancer
Flow Laboratories	71-2097	Complete characterization of RNA and DNA viruses and viral antigens in mammalian tumors
Georgetown University	65-53	Studies on Type B particles associated with human breast cancer
George Washington Univ.	72-3251	Cell-mediated immunity to human cancers
Howard University	70-2178	Cell-mediated immunity to human cancers
IARC	70-2076	Seroepidemiological studies of Burkitt's lymphoma, NPC
Institute for Med. Res.	68-1000	Studies on Type B particles associated with human breast cancer
Jackson Labs	67-744	Natural occurrence of RNA tumor viruses and host gene control of virus expression

TABLE II Analysis of Contracts by Activity

Phase III-A: COMPLETE CHARACTERIZATION AND DEFINITION OF PRESUMPTIVE DISEASE RELATIONSHIPS (continued)
Step 1: PRESUMPTIVE DISEASE RELATIONSHIP

Contractor	Cont. No.	Description of Work
Jewish Hospital	72-2034	Relationship of chromosomal abnormalities to susceptibility to cancer and viral transformation
Johns Hopkins Univ.	71-2121	Studies on the relationships of Herpes simplex type II to cervical carcinoma
Karolinska Institute	69-2005	Immunological studies on the etiology of EBV-associated diseases
Life Sciences	69-63	Studies on Marek's disease Herpes virus
Litton-Bionetics	71-2025	Biochemical studies on relationship of Type C viruses to human leukemia
iiversity	67-47	Epidemiological studies on role of EBV in Burkitt's lymphoma
Hospital	72-2012	Interaction of oncogenic viruses and host immune mechanisms; relationship of immunological competence and viral carcinogenesis
oratories	72-2006	Biochemical studies on relationship of Type C viruses to human leukemia and sarcoma
iversity	67-1187	Immunological responses in avian tumor virus infection
ological Assoc.	70-2068	Evaluation of cocarcinogenic factors in viral oncogenesis
ological Assoc.	67-697	Type C virus antigen expression during embryogenesis and in spontaneous cancers
ota, Univ. of	69-2061	Immunologic evaluation of host response to human tumors
, Univ. of	71-2056	Isolation and characterization of Herpes simplex virus-induced antigens
rlands Cancer Inst.	72-3260	Determination of natural route of infection of MTV

TABLE II Analysis of Contracts by Activity

Phase III-A: COMPLETE CHARACTERIZATION AND DEFINITION OF PRESUMPTIVE DISEASE RELATIONSHIPS (continued)
Step 1: PRESUMPTIVE DISEASE RELATIONSHIP

Contractor	Cont. No.	Description of Work
New York Med. College	72-3289	Immunopathology of human breast cancer
Ohio State University	65-1001	Determination of immune response to viral antigens in model systems
Pennsylvania State	70-2024	Effect of cocarcinogens on oncogenic potential of human viruses
Robert B. Brigham	71-2172	Immunologic evaluation of host response to viral antigens in model systems
Rutgers, The State Univ.	71-2077	Relationship of presumed non-oncogenic agents to cancer induction
Salk Institute	72-3207	Immunologic studies on host reaction to viral antigens
Southern Calif., Univ. of	68-1030	Possible role of animal tumor viruses, environmental cocarcinogens
Texas, Univ. of	71-2178	Immunologic studies on host reaction to tumor antigens
Texas, Univ. of	72-3262	Determination of host reaction to murine leukemia virus antigens in human cancer patients
Washington, Univ. of	71-2171	Immunologic reactivity to tumor antigens in patients with various malignancies
Washington, Univ. of	72-2037	Immunologic reactivity to canine sarcomas
Wisconsin, Univ. of	72-2022	Development and improvement of methods for the detection and quantitation of immunity to oncogenic viruses and viral antigens

TABLE II Analysis of Contracts by Activities

PHASE III-A: COMPLETE CHARACTERIZATION AND DEFINITION OF PRESUMPTIVE DISEASE RELATIONSHIPS
Step 2: COMPLETE CHARACTERIZATION

Contractor	Cont. No.	Description of Work
Columbia Univ.	70-2049	Biochemical characterization of oncogenic viruses
Flow Laboratories	71-2097	Biochemical, biophysical and immunologic characterization of oncogenic viruses
Karolinska Institute	69-2005	Immunological characterization of EBV
Life Sciences	69-63	Biological characterization of MDHV
Meloy Laboratories	72-2006	Biochemical, biophysical and immunologic characterization of oncogenic viruses

TABLE II Analysis of Contracts by Activity

Phase III-B: COMPLETE CHARACTERIZATION: DEMONSTRATION OF VIRUS-MEDIATED FUNCTIONS ESSENTIAL FOR INDUCTION AND MAINTENANCE OF NEOPLASIA

Contractor	Cont. No.	Description of Work
California, Univ. of	71-2147	Biochemical determination of viral gene expression (molecular hybridization)
California, Univ. of	72-3226	Molecular hybridization studies of human cancers
Columbia University	70-2049	Search for specific viral gene expressions in human cancer
Einstein Coll. of Med.	71-2251	Determine molecular pathways of oncogenic virus expression
Life Sciences, Inc.	69-63	Co-carcinogenic factors in the etiology of Marek's disease
Mass. Gen. Hospital	71-2174	Complete characterization of oncogenic viral nucleic acids
Mass. Inst. of Tech.	71-2149	Determine the nature of oncogenic viral gene expression
Meloy Laboratories	72-2006	Molecular hybridization studies on human cancers
North Carolina, Univ. of	72-3228	Molecular hybridization studies of human leukemia and lymphoma
Pub. Health Res. Inst.	71-2129	Characterization of the specific membrane changes associated with oncogenic virus transformation
St. Louis University	67-692	Search for specific viral gene expressions in human cancer

TABLE II Analysis of Contracts by Activity

Phase IV-A: IMMUNOLOGICAL CONTROL
Step 1: DETERMINE SUITABLE IMMUNOLOGICAL CONTROL

Contractor	Cont. No.	Description of Work
Health Res. Inc.	72-2014	Evaluation of neuraminidase-treatment to enhance tumor cell immunogenicity
Johns Hopkins Univ.	71-2109	Evaluation of methods for monitoring immune responses of cancer patients
Meloy Laboratories	72-2020	Evaluation of various approaches to immunotherapy in model systems
Microbiological Assoc.	70-2068	Evaluation of viral vaccines and interferons in the protection against chemically-induced neoplasms
Merck and Co.	71-2059	Developmental research for virus vaccine production
Res. Fdn. of State of New York	71-2137	Clinical studies on enhancement of tumor immunity
Texas, Univ. of	72-3260	Evaluation of viral vaccines in the treatment of human leukemia/lymphoma

TABLE II Analysis of Contracts by Activity

Phase IV-B: BIOCHEMICAL CONTROL
Step 1: DETERMINE SUITABLE METHODS FOR BIOCHEMICAL CONTROL

Contractor	Cont. No.	Description of Work
St. Louis University	67-692	Screening of various chemicals as inhibitors of polymerases

RESOURCES

Contractor	Number	Type	Species
Biolabs, Inc.	72-2068	virus	human
California, University of	70-2202	animal	feline
California, University of	63-13	tissues	human
Chicago Park District	65-1017	animal	primates
Colorado, University of	69-2080	tissues, sera	human
Connecticut, Univ. of	69-52	animal	SPF chickens
Cornell University	70-2224	service	feline
Dow Chemical	65-1045	service	
Duke University	71-2132	virus	avian
Electronucleonics	71-2253	virus	animal
Emory University	71-2256	animal	primate
Flow Laboratories	71-2341	animal	rodent
Flow Laboratories	65-1012	repository	murine
Georgetown University	72-3248	tissue	human
Germfree Life Research Center	72-3261	animal	avian, rodent
Health Research	72-3247	tissue	human
Hospital for Sick Children	65-97	tissues	human
Huntingdon Research Center	69-54	service	
Johns Hopkins University	69-2008	animal	chicken
Life Sciences	68-711	animal	chicken
Litton Bionetics	71-2025	animal	primates
Louisville, University of	66-902	virus	primates
Meloy Laboratories	72-3202	virus	murine
Meloy Laboratories	72-2306	animal	primates
Memorial Hospital	71-2116	tissues, sera	human
Memorial Hospital	71-2194	sera	human
Michigan Cancer Fdn.	71-2421	tissues	human
Michigan, University of	65-639	tissues	human
Microbiological Associates, Inc.	69-914	animal	murine
Microbiological Associates, Inc.	67-700	service	murine
Minnesota, University of	72-2066	service	
Montreal Children's Hospital	65-1020	tissues, sera	human

RESOURCES

Contractor	Number	Type	Species
Naval Biological Laboratory	FS-8	service	
Padua, University of	68-1389	tissues	human
Pfizer, Chas. and Co.	70-2080	virus	animal, human
Southwest Foundation	69-93	service	simian
Southwest Foundation	69-2011	animal	primate
Stanford University	69-2053	PPLO testing; tissue	human
University Labs	66-1133	virus	animal
Wolf Res. and Development Corp.	71-2270	service	

TABLE III
ALPHABETICAL LISTING OF CONTRACTS
AND INDEX TO CONTRACT NARRATIVES

CONTRACTOR	FUNCTIONS[1/]	PAGE
Aichi Cancer Center (69-0096)	I (1,2,3); II-B (1)	123
Atomic Energy Commission (FS-7)	I (3)	175
Atomic Energy Commission (FS-13)	I (3); II-B (1,2); III-A (1)	314
Auerbach Assoc. (72-2023)	I (2)	193
Baylor College of Medicine (72-2058)	II-B (1)	324
Baylor University (68-0678)	I (1,2,3); II-A (1,2); III-A (1)	124
Biolabs, Inc. (72-2068)	II-A (1); Resources	194
California SDPH (68-0997)	1 (3); II-A (1); II-B (1); III-A (1)	250

1/ For description of research activities, see Research Logic Chart for SVCP inside back cover and Table II, page 81.

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
California SDPH (69-0087)	I (1)	252
California, University of (63-0013)	I (3); II-A (1); II-B (1); Resources	197
California, University of (70-2048)	I (3); II-A (1,2)	257
California, University of (70-2202)	Resources	198
California, University of (71-2147)	II-B (2); III-B	253
California, University of (71-2173)	II-B (2)	319
California, University of (72-2008)	I (1,2,3)	167
California, University of (72-2080)	II-A (1)	308
California, University of (72-3226)	III-B	313
California, University of (72-3236)	II-B (2)	312

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Center for Disease Control (VCL-42)	I (1,2)	172
Chicago Park District (65-1017)	Resources	199
Children's Hospital of D.C. (72-2071)	III-A (1)	174
Children's Hosp. of Phila. (66-0477)	I (1,3); II-A (1,2); III-A (1)	168
Colorado, University (69-2080)	I (2); Resources	200
Columbia University (70-2049)	I (3); II-A (2); II-B (2); III-A (1,2); III-B	125
Connecticut, University of (69-0052)	Resources	201
Cornell University (70-2224)	I (3); Resources	202
Cornell University (71-2508)	I (3); II-A (1,2)	126
Dow Chemical Company (65-1045)	Service	236

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Duke University (71-2132)	II-A (1,2); Resources	204
Einstein Medical College (65-0612)	I (3); III-A (1)	259
Einstein Medical College (71-2251)	II-B (2); III-B	128
Electro-Nucleonics (71-2253)	II-A (1); Resources	206
Electro-Nucleonics (72-3249)	Resources	207
Emory University (71-2256)	Resources	208
Emory University (72-2301)	II-A (1,2); III-A (1)	155
Flow Labs, Inc. (65-1012)	Resources	209
Flow Labs, Inc. (71-2097)	I (3); II-A (1,2); II-B (1,2); III-A (1,2)	260
Flow Labs, Inc. (71-2341)	Resources	209

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
George Washington University (72-3251)	III-A (1)	174
Georgetown University (65-0053)	I (1,2,3); III-A (1)	295
Georgetown University (72-3248)	Resources	211
Germfree Life Res. Center (72-3261)	Resources	212
Harvard University (72-3246)	I (3); II-A (1,2)	313
Hazleton Laboratories, Inc. (69-2079)	I (3); II-A (1,2); II-B (1,2)	130
Health Research, Inc. (72-3247)	Resources	214
Health Research, Inc. (72-2014)	IV-A (1)	162
Hôpital St. Louis (72-3263)	II-B (1)	157
Hospital for Sick Children (72-3266)	I (2), Resources	214

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Howard University (70-2178)	I (2,3); III-A (1)	296
Huntingdon Research Center, Inc. (69-0054)	I (3), Resources	215
Illinois, University of (72-2031)	II-B (1)	325
Indiana University (69-2048)	I (3); II-A (2)	187
Institute for Medical Research (68-1000)	I (1,3); III-A (1)	298
Int'l Agency for Res. on Cancer (70-2076)	I (1,2,3); II-A (1,2); III-A (1)	170
Jackson Laboratory (67-0744)	I (3); III-A (1)	263
Jewish Hospital (72-2034)	I (1,2); III-A (1)	323
Johns Hopkins University (69-2008)	Resources	217
Johns Hopkins University (71-2109)	I (2,3); IV-A (1)	161

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Johns Hopkins University (71-2121)	I (1,3); III-A (1)	131
Karolinska Institute (69-2005)	I (1,2,3); II-A (1,2); III-A (1,2)	132
Life Sciences, Inc. (68-0711)	Resources	217
Life Sciences, Inc. (69-0063)	II-A (1,2); III-A (1,2); III-B	133
Litton/Bionetics, Inc. (69-2160)	I (3); II-B (1); III-A (1)	326
Litton/Bionetics, Inc. (71-2025)	I (3); II-A (1); III-A (1); Resources	195
Louisville, University of (66-0902)	Resources	219
Makerere University College (67-0047)	I (1,2); III-A (1)	178
Mason Research Institute (70-2204)	I (3); II-A (1)	300
Massachusetts Instit. Tech. (71-2149)	II-B (2); III-B	322

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Mass. General Hospital (71-2174)	II-B (2); III-B	134
Mass. General Hospital (72-2012)	III-A (1)	136
Medical College of Wisconsin (68-1010)	II-A (1); II-B (1)	302
Meloy Labs, Inc. (72-2006)	I (3); II-A (1,2); II-B (1,2); III-A (1,2); III-B	190
Meloy Labs, Inc. (72-2020)	IV-A (1)	188
Meloy Labs, Inc. (72-2306)	Resources - see also Emory Univ. 72-2301	160
Meloy Labs, Inc. (72-3202	I (3); II-A (1,2); Resources	220
Memorial Hospital (N.Y.) (71-2194)	I (2); Resources	303
Memorial Hospital (N.Y.) (71-2116)	I (2); Resources	222
Merck & Company, Inc. (71-2059)	IV-A (1)	139

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Miami, University of (67-1187)	III-A (1)	183
Miami, University of (70-2211)	II-A (1); II-A (2)	185
Michigan Cancer Foundation (71-2421)	I (1,2,3); Resources	304
Michigan, University of (65-0639)	I (2); Resources	223
Microbiological Associates, Inc. (66-0914)	Resources	224
Microbiological Associates, Inc (67-0697)	I (3); II-A (1); II-B (1); III-A (1)	266
Microbiological Associates, Inc. (67-0700)	I (3); Resources	225
Microbiological Associates, Inc. (70-2068)	I (3); II-A (1,2); II-B (1,2); III-A (1); IV-A (1)	268
Minnesota, University of (69-2061)	I (3); III-A (1)	173
Minnesota, University of (71-2261)	I (1,2,3)	317

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Minnesota, University of (72-2066)	Biohazards Training Course	247
Montreal Children's Hospital (72-3277)	I (2); Resources	227
Naples, University of (71-2056)	III-A (1)	141
National Academy of Sciences (64-0044)	Scientific Meeting	*
Naval Biological Laboratories (FS-57)	II-A (1)	242
Naval Biomedical Research Labs (FS-08)	Service	197
Netherlands Cancer Institute (72-3260)	I (3); III-A (1)	310
New York Medical College (72-3289)	III-A (1)	177
North Carolina, University of (72-3228)	II-B (2); III-B	150

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
North Dakota, University of (66-0008)	II-A (1)	181
Ohio State University (65-1001)	I (3); II-A (1); III-A (1)	238
Ohio State University (69-2233)	I (3)	143
Oregon State University (71-2175)	II-B (2)	144
Padova, University of (68-1389)	I (2); Resources	227
Pennsylvania State University (70-2024)	I (3); II-A (1,2); II-B (2); III-A (1)	145
Pennsylvania, University of (65-1013)	I (3); II-A (1); II-A (2)	147
Pfizer, Charles Inc. (67-1176)	I (3); II-A (1,2)	305
Pfizer, Charles Inc. (70-2080)	II-A (1); Resources	228
Princeton University (71-2372)	I (3); II-B (2)	274

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Public Health Res. Instit. (71-2129)	I (3); II-B (1,2); III-B	148
Public Health Res. Instit. (72-2028)	II-B (2)	324
Res. Fdn., St. Univ. of N.Y. (71-2137)	IV-A (1)	164
Robert B. Brigham Hospital (71-2172)	I (3); III-A (1)	165
Rush-Presbyterian Hospital (71-2032)	I (3); II-A (1,2)	149
Rutgers University (71-2077)	III- A (1)	151
Salk Institute (67-1147)	I (3); II-B (1)	278
Salk Institute (72-3207)	I (3); III-A (1)	294
Scripps Clinic and Res. Fdn. (72-3264)	I (3); II-A (2); II-B (2)	256
Southern California, Univ. of (68-1030)	I (1,2,3); II-A (1,2); II-B (1,2); III-A (1)	279

TABLE (continued)

CONTRACTOR	FUNCTIONS	PAGE
Southern California, Univ. of (72-2032)	II-B (1,2); III-B	284
Southwest Foundation (69-0093)	Resources	231
Southwest Foundation (69-2011)	Resources	231
Southwest Foundation (71-2348)	II-A (1)	245
St. Joseph's Hospital (69-2074)	I (2,3)	230
St. Jude's Hospital (71-2134)	II-A (1,2)	152
St. Louis University (67-0692)	I (3); II-A (1,2); II-B (2); III-B; IV-B	275
Stanford University (69-2053)	I (3); II-B (1); Resources	286
Tel Aviv University (72-3237)	I (3); II-B (1,2)	307
Texas, University of (65-0604)	I (1,2,3); II-A (1,2); II-B (1,2)	154

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Texas, University of (71-2178)	I (3); III-A (1)	163
Texas, University of (72-3262)	III-A (1); IV-A (1)	177
Texas, University of (71-2135)	I (1)	249
TRW Systems Group (70-2200)	II-A (2)	165
University Labs, Inc. (66-1133)	II-A (1); Resources	232
Washington, University of (71-2171)	I (3); III-A (1)	288
Washington, University of (72-2037)	III-A (1)	184
Weizmann Institute (69-2014)	I (3); II-B (2)	290
Wisconsin, University of (72-2022)	I (3); II-A (2); II-B (2); III-A (1)	316
Wistar Institute (71-2092)	I (3); II-A (2)	291

TABLE III (continued)

CONTRACTOR	FUNCTIONS	PAGE
Wolf Research (71-2270)	Service	233
World Comm. for Comparative Leukemia Research (71-1033)	Scientific Meeting	*
Worcester Foundation for Experimental Biology (69-2007)	I(3); II-A(2)	293

* Money made available for scientific meeting. No Report.

C. CONTRACT PROGRAM

4. Contract Summaries

DEVELOPMENTAL RESEARCH PROGRAM SEGMENT

Dr. Robert A. Manaker, Acting Chief, VBB, DCCP, Chairman
Dr. Michael A. Chirigos, Associate Chief, VBB, DCCP, Vice Chairman

AICHI CANCER CENTER (NIH-69-96)

Title: Virus Rescue Studies in Human Leukemia/Lymphoma Cell Lines

Contractor's Project Director: Dr. Yohei Ito

Project Officer (NCI): Dr. Charles W. Boone

Objectives: (1) To investiage the possible role of Herpes type virus and C-type viruses as etiological agents of human neoplasia, involving the establishment and investigation of numerous human suspension and monolayer cell lines by electron microscopy, immunofluorescence, and other techniques. (2) To make available to the Special Virus Cancer Program human embryonic tissues and high-titer anti-herpes human antiserum.

Major Findings: Nineteen suspension culture lines and about 80 monolayer culture lines were established from tissues of human patients with leukemia, Hodgkin's disease, lymphosarcoma and nasopharyngeal carcinoma. EB virus was identified in the suspension culture lines but was absent in monolayer cell cultures. No C-type viruses were found in any culture.

Over 700 sera from patients with different neoplasms were examined for antibody titers against EBV. Only those with Burkitt tumor, infectious mononucleosis, and nasopharyngeal carcinoma were found to possess high antibody titers.

Significance to Biomedical Research and the Program of the Institute: Since this project is located in the Far East, comparative data acquired in Orientals complements observations made on Caucasian populations. The Principal Investigator has verified observations made in this country and in Europe on the distribution of antibody to Epstein-Barr virus in different neoplastic diseases, and is also engaged in studies on tumors in Orientals which are relatively rare in this country.

Proposed Course: The contractor will emphasize ongoing studies related to the determination of viral reverse transcriptate activity and virus-related nucleic acids in human mammary carcinoma.

Date Contract Initiated: May 2, 1969

Current Annual Level: $40,000

BAYLOR COLLEGE OF MEDICINE (PH43-68-678)

Title: Studies on Viruses as Related to Cancer

Contractor's Project Director: Dr. Joseph Melnick

Project Officers (NCI): Dr. Robert A. Manaker
Dr. Michael A. Chirigos

Objectives: To determine the relationship of viruses to selected neoplasias and their significance in the neoplastic process.

Major Findings: The application of the Cr 51 release cytotoxicity test has demonstrated that the sera of leukemic children contain low levels of antibody reactive with their autologous peripheral blood leukocytes taken during relapse but not to their leukocytes taken during remission. Preliminary studies suggest that cytotoxicity tests may permit specific detection of herpesvirus type 2 antibodies in sera absorbed with cells infected with herpesvirus type 1. The method may be of value in studies on the relationship of HSV-2 to cervical carcinoma. Present testing procedures show the incidence of antibodies to HSV-2 in Caucasian and Negro women in the Houston area to be more than twice that in control women of similar ages and social levels.

Comparative studies on HSV-1 and HSV-2 showed a 70% homology between their DNAs. Recombination experiments on temperature sensitive (ts) mutants of HSV-1 falling into 8 complementation groups revealed recombination frequencies of up to 50 percent with complementing mutant pairs. Non-complementing pairs either failed to recombine or recombined in low frequencies. A defect in some ts mutants in ability to induce synthesis of thymidine kinase was independent of the ts defect. At the non-permissive temperature, one HSV-1 ts mutant accumulates a polypeptide (C-3). This offers the possibility of determining the role of this polypeptide in herpesvirus replication. Thirteen ts mutants of HSV-2 are under study.

Seventeen papers were published during the past contract year on research conducted under this contract.

Significance to Biomedical Research and to the Program of the Institute: This contractor provides a progressive program of research to determine possible etiological relationships of viruses to human cancer. Evidence of possible relationships has been sought by the study of the immune responses of patients and their associates to tumor antigens. Important contributions to Program have been made by the contractor's investigations on genital herpesvirus type 2 associations with malignant carcinoma of the cervix. The importance of herpesviruses in neoplastic processes is evident from the recognition of lymphoproliferative diseases induced by herpesvirus infections as well as a strong association with the development of carcinoma. This contract provides for fundamental studies on herpesviruses which may be invaluable as the role of these agents in precipitating oncogenic processes is further defined.

Proposed Course: The studies relating to childhood leukemia and intensive studies on herpesviruses as agents of apparent importance in oncogenesis will continue.

Date Contract Initiated: June 27, 1963

Current Annual Level: $754,000

COLUMBIA UNIVERSITY (NIH-70-2049)

Title: Replication of Oncogenic RNA Viruses and its Relation to Human Cancer

Contractor's Project Director: Dr. Sol Spiegelman

Project Officers (NCI): Dr. Timothy O'Connor
Dr. Robert A. Manaker

Objectives: To study RNA tumor viruses at molecular levels to elucidate mechanisms whereby they induce neoplastic transformation of cells and to apply this knowledge to the determination of viral relationships in human neoplasms and ultimately to the selection of measures for control of the neoplastic process.

Major Findings: The RNA-dependent DNA polymerase activity was found in the virions of eleven different groups of RNA viruses that cause leukemias or sarcomas, or have been associated with mammary tumors, in different animal species. A DNA-instructed polymerase activity was also found in the virions of all oncogenic viruses examined. By using synthetic polynucleotide duplexes, it was established that oncogenic viruses contain DNA polymerase activities directed by single- and double-stranded RNA, double-stranded DNA, and DNA-RNA hybrids. These activities were shown to be exhibited by a single enzyme. Avian myeloblastosis virus (AMV) reverse transcriptase gave greater dT-primed synthesis with poly rA than with poly dA strands. This appeared to be a means of distinguishing this enzyme from the normal cellular polymerases. By this criterion, enzymic activity was detected in over 120 leukemic buffy coat specimens and in none of 70 buffy coats from normal patients nor in leukoproliferations in diseases other than leukemia. Similar polymerase activity was found in embryonic tissues of animals and man. The highest activities were detected in tissues obtained early in embryogenesis. Further experience showed that every proliferating cell has an elevated response to a dC:dG template, but not all respond to dT:rA and rA:rU.

The purified reverse transcriptase from AMV was shown to consist of two subunits of 110,000 and 69,000 molecular weight respectively, and to be free of ribonuclease and DNA endonuclease activity.

The search for enzymatic evidence of oncogenic RNA viruses in human milk, plasma or tissue is complicated by the low viral content in the presence

of large amounts of enzymatically active debris. A procedure was developed whereby the presence of reverse transcriptase and 70S RNA could be demonstrated in such specimens. The method demonstrated that particles detected in human milk possess these two features characteristic of RNA tumor viruses.

Labeled DNA complementary to oncogenic virus RNA provided a probe to search for RNA in tumor tissues homologous to nucleotide sequences in the viral RNA. RNA extracted from the polysome fraction of 19 of 29 specimens of human mammary carcinoma tissue hybridized with the DNA probe prepared from mouse mammary tumor virus (MTV) RNA but not with DNA complementary to AMV or Rauscher mouse leukemia virus (RLV). No significant hybridization was detected between MTV DNA and polysome RNA extracted from normal adult or benign breast tumor tissue. Further study showed RNA nucleotide sequences homologous to RLV RNA but not to AMV RNA or MTV RNA to be present in the polysome fraction of human leukemic white blood cells and of human sarcomas. No such RNA was recovered from control tissues.

Ten recent publications appeared or are in press describing the observations made in this laboratory.

Significance to Biomedical Research and to the Program of the Institute: This contractor has pursued a systematic course of research to develop and apply molecular biological methods to demonstrate viral relationships to human tumors. The observations made open new avenues for exploration and development in the study of virally-induced oncogenic processes and their relationship to the spontaneously recurring neoplasms in man.

Proposed Course: The investigations underway will be continued to acquire additional data on the polymerase activities detected in normal embryonic and tumor tissue. The initial studies on the existence of RNA nucleotide sequences in polysomal fractions of human tumor cell which are homologous to the RNA of known animal tumor viruses require further investigations to determine the significance of the observation and expansion of the primary work to other human tumors and virus systems.

Date Contract Initiated: October 29, 1969

Current Annual Level: $800,000

CORNELL UNIVERSITY (NIH-71-2508)

Title: Leukemia Studies in the Cat

Contractor's Project Director: Dr. Charles Rickard

Project Officers (NCI): Dr. Michael A. Chirigos
Dr. Robert A. Manaker

Objectives: To determine mechanisms for transmission of oncogenic viruses in cats and to investigate the possibility of natural infection of humans

by feline viruses.

Major Findings: A suspension type culture of thymic cat tissue has continuously produced FeLV of high particle count per unit volume. Virus was supplied to other investigators and was used for studies on the group-specific antigens of the virion. Antigens have been purified by preparatory electrophoresis and Sephadex chromatography for use in preparing serological reagents. These reagents are considered sufficiently specific for use in sensitive tests to attempt to demonstrate the presence of gs-3 or feline gs-specific antigens in human cancer cells.

FeLV from clones of infected cells was used to produce antisera to fresh undisrupted virus particles. Quantitative assay systems for virus infectivity were compared. Neutralization tests showed that many normal or leukemic cats have serum antibodies neutralizing sub-group A virus. Tests will be conducted to test human sera for antibody against each serotype of the feline C-type viruses.

Some cats with leukemia or related neoplasms have precipitating serum antibody reacting with an unidentified antigen of cat leukemia virus. Sera from some clinically normal cats and some cats in the SPF colony free of conventional cat viruses possess similar precipitating antibody. The antibody appears to be passively transmitted through colostrum. Precipitin-positive sera from normal or SPF cats reacting with this antigen do not give a line of identity with antisera against gs-interspecies or feline gs-species antigens when set up in agar gel tests against disrupted FeLV. The significance of this immunoprecipitin reaction will be sought.

Sera of 8 normal cats which were pets of humans with leukemia were negative in tests for infection by the known feline leukemia viruses. A feline virus was isolated from a cat with lymphosarcoma which was the pet of a human leukemic. In gel diffusion tests against the undisrupted virus isolate, another FeLV serotype, a feline sarcoma virus, and feline group-specific antigens, a five-fold concentrate of the human patient's plasma gave negative results. Sera from 3 members of the patient's household were also negative.

Crandell's continuous feline kidney cell line (CCC) was found useful for assay of FeLV, FeSV, and MSV(FeLV). DEAE-dextran pretreatment enhanced focus formation. The CCC line has shown no evidence of "spontaneous" C-type virus production or gs antigens.

For experimental induction of canine lymphosarcoma by FeLV, age susceptibility is a critical factor. Puppies become refractory within 2-3 days after birth. Time to tumor is substantially decreased by *in utero* inoculation, and virus can be demonstrated in the neoplastic tissue. No virus was detected in puppies born to a female inoculated with FeLV 9 days before delivery suggesting that transplacental infection does not occur.

In other studies it was found that fetal or neonatal dogs inoculated with feline liposarcoma virus developed no neoplasms. Myelocytic leukemia was transmitted from a spontaneous case in a cat to 2 kittens which developed

myelocytic leukemia with abundant C-type particles after 9 months. This virus was inoculated into fetal dogs 16 days before birth. At 5 weeks after birth, there was no evidence of transmission. Fetal inoculation of cats with canine transmissible venereal tumor and canine mast cell tumor was accomplished. Animals are under observation to determine possibility of rescue on oncogenic dog virus genome by the cat.

Significance to Biomedical Research and the Program of the Institute: The cat offers opportunity to determine mechanisms of infection and perpetuation of oncogenic viruses in a natural population. Comparative studies between viruses naturally afflicting different animal species can contribute to an understanding of mechanisms involved in virus-induced cell transformation. The cat viruses infect and reproduce in cells of animal species other than the cat, as well as in human cells. Since the cat is a common household pet, and viral relationships in spontaneous neoplasms have not yet been completely defined, further studies are necessary to determine whether cat viruses may infect humans, particularly children, by contacts in the household.

Proposed Course: Highly specific antisera to the feline viral antigens will be prepared. Serological tests will be applied to experimental and natural cat populations to obtain evidence for possible horizontal transmission of virus infection. Human sera will be tested against the different strains of virus for evidence of human infection. In spontaneous neoplasms of the cat where there is no evidence of the presence of recognized sub-group viruses, efforts will be made to determine whether an unrecognized sub-group is involved. Virus detected or induced in fetal tissues will be compared with the recognized serotypes. Selected canine neoplasms will be studied by different techniques to determine whether the presence of virus may be recognized. Collaborative studies will be conducted with other investigators for evidence of antigenic relationsips between neoplasms of dogs and human patients. The only virus known to produce mammary tumors experimentally is the mouse mammary tumor virus as an important tool for further investigations.

Date Contract Initiated: June 23, 1965

Current Annual Level: $445,500

ALBERT EINSTEIN COLLEGE OF MEDICINE (NIH-71-2251)

Title: Studies on the Molecular Basis of Viral Carcinogenesis

Contractor's Project Director: Dr. J. Thomas August

Project Officers (NCI): Dr. Timothy O'Connor
Dr. Robert A. Manaker

Objectives: To determine the molecular events involved in the adsorption and penetration of oncogenic viruses into host cells, in malignant transformation of cells, and in viral replication.

Major Findings: During the first year tissue culture systems were developed for the study of Friend leukemia virus replication in permissive and non-permissive cells with the aim of determining the mechanism of restriction. Temperature sensitive virus mutants are being selected to help define viral genes responsible for replication and malignancy.

Enzyme studies have shown the presence of a protein kinase within the viruses. This enzyme differs from cellular enzyme and phosphorylates most of the structural proteins of the virion as well as some host cell proteins.

The reverse transcriptase extracted from AMV and RLV, when highly purified, yielded an RNA-DNA hybrid as its sole product. To act catalytically in producing free DNA an AMV endonuclease was required. The transcription of DNA from AMV RNA was increased 10-fold when extracts of AMV were added to the purified enzyme. Fifty percent of the DNA product was single-stranded. Evidence indicates the reverse transcriptase to be a repair type enzyme, and new DNA complementary to the RNA template is covalently bound to the terminal of the DNA primer. Thus, present evidence suggests the reverse transcriptase is not directly involved in the replication of the RNA of tumor viruses.

Significance to Biomedical Research and the Program of the Institute: The studies initiated in the contractor's laboratory are designed to investigate host factors restricting or permitting penetration and replication of oncogenic virus and to probe biochemical events key to viral replicative processes and cellular transformation.

Proposed Course: The virion protein kinase will be purified as a first step to characterization of the enzyme and its biological role in virus infection. The mechanism of cell transformation will be investigated in the Schmidt Ruppin Rous sarcoma virus system. Sensitive quantitative assays of events associated with the transformation process are required. Pathways of carbohydrate metabolism and the time course of appearance of new cell antigens will be explored. To answer questions on the nature of antigenic determinants of the tumor viruses, the first step will be isolation and characterization of the interspecies specific antigen of Rauscher and feline leukemia viruses. Agents which lead to the stimulation of reverse transcription have been partially purified and will be further characterized. Attempts are underway to determine whether the RNA of RLV and AMV contain different or identical 30S subunit components. This information will aid in evaluating the amount of genetic information available for coding in the RNA oncogenic viruses. Studies have commenced on the mechanism of replication of viral RNA. The reverse transcriptase does not appear to be directly involved. Studies are continuing on the synthesis of host cell membrane glycoproteins in infected and uninfected cells. Attempts are being made to purify N and B strains of Friend virus as a preliminary to comparison of their composition. Temperature sensitive Friend virus mutants will be selected and utilized for genetic and biochemical studies directed to elucidation of viral and cellular factors contributing to neoplastic change.

Date Contract Initiated: April 26, 1971

Current Annual Level: $536,000

HAZELTON LABORATORIES, INC. (NIH-69-2079)

Title: Studies on the Etiology of Canine Cancer

Contractor's Project Director: Dr. Erling M. Jensen

Project Officers (NCI): Dr. Michael A. Chirigos
Dr. Robert A. Manaker

Objectives: To determine whether any canine cancer is caused by viruses and whether there is any possible etiological relationship between canine and human cancers.

Major Findings: A common antigen in several specific canine sarcomas was detected by immunofluorescence tests with sera from the tumor-bearing and other sarcomatous dogs. Successful transplantation of a canine mammary carcinoma was achieved by inoculation of beagles in utero. If continuous passage proves possible, the tumor will provide a valuable system for studies on viral etiology, therapy, and possibly hormonal influence on tumor development. Cells of a canine osteosarcoma inoculated into kittens in utero were recovered after birth of the animals and placed in culture. Attempts are underway to determine whether this procedure activated virus production.

A convenient, quantitative infectivity focus assay for feline virus was developed for studies using feline leukemia viruses in attempts to recover defective viruses from canine tumors. Treatment with BUdR and IUdR was introduced in attempts to induce virus release from canine tumor cells. Exposure of XC rat cells, which have been routinely used to titer murine leukemia viruses, to BUdR activated virus production. Two viruses appear to be present.

Studies were initiated to evaluate the effect of combined chemotherapy and nonspecific immune stimulators on spontaneous lymphosarcoma in dogs. In some preliminary tests, streptonigrin was used to determine its inhibitory effect on dog cells infected with feline leukemia virus. Even at toxic drug levels, the reproduction of the virus was not eliminated. Focal areas of morphological change were observed in the canine cells exposed to streptomycin.

Significance to Biomedical Research and the Program of the Institute: Study of canine neoplasms for evidence of viral associations is important in several respects. Since humans are in close contact with canine pets, the possibility that they may be exposed to a canine tumor virus must be investigated. In contrast to the cat and mouse, viruses are not regularly shed by canine tumor cells. An analogous situation exists in the human. The dog provides an excellent experimental animal to determine the presence

of covert viral infections contributing to neoplastic transformations. If such viral relationships to cancer in the dog can be firmly established, the dog will provide opportunity to study the mechanisms for transmission of infection, virus-host relationships, and evaluation of control measures. In this respect, the dog would be one of the best models for human cancer.

Proposed Course: Redirection of the effort in this laboratory is being considered to utilize the facilities for more intensive study on tumor viruses, a more concentrated effort on viral relationships to canine mammary carcinoma, and evaluation of immunotherapeutic approaches to control of naturally occurring neoplasms.

Date Contract Initiated: May 26, 1969

Current Annual Level: $400,000

JOHNS HOPKINS UNIVERSITY (NIH-71-2121)

Title: Herpesvirus Antigens and Virions in Neoplastic Cells from Squamous Carcinoma of the Human Cervix

Contractor's Project Director: Dr. L. Aurelian

Project Officers (NCI): Dr. Charles W. Boone
Dr. Robert A. Manaker

Objectives: The ultimate objective of this project is the development of evidence for/or against virus as a factor in the etiology of carcinoma of the human uterine cervix. The immediate objective is the identification of Herpes simplex virus type II (HSV-2) antigens and virions in neoplastic cells.

Major Findings: Over 90% of patients with epithelial atypia, carcinoma in situ, or invasive carcinoma of the cervix possessed antibodies to HSV-2 in contrast to positive findings in only 55% of a matched control population. HSV-2 antigens were detected in the cytoplasm of exfoliated dyskaryotic cells of cancer patients by immunofluorescence. In tumor biopsies, no evidence of virus particles or antigens were detected. Cultured cells from a cervical carcinoma could be induced to release virus by raising the pH of the culture medium.

Significance to Biomedical Research and the Program of the Institute: An important question relevant to total program is whether Herpes viruses are directly responsible for oncogenesis or whether infections activate a pre-existing premalignant state. The Special Virus Cancer Program is concentrating on studies of neoplastic diseases in man and animals in which Herpes virus involvement has been demonstrated in order to define a specific role, if any, for this group of viruses in the neoplastic process. If genital Herpes virus infection can be definitely shown to be a factor in the development of cervical neoplasia, appropriate control measures may be developed to reduce the incidence of this cancer in man.

Proposed Course: The contractor will compare antigens in cervical carcinoma cells with those induced in Hep-2 by Herpes simplex virus type I and II. Work will continue on the characterization of HSV-2 antigens present in exfoliated cancer cells from patients with cervical cancer.

Date Contract Initiated: May 5, 1971

Current Annual Level: $92,000

KAROLINSKA INSTITUTE (NIH-69-2005)

Title: Studies on the Significance of Herpes-type Virus in the Etiology of Some Human Cancers

Contractor's Project Director: Dr. George Klein

Project Officers (NCI): Dr. Charles W. Boone
Dr. Gary R. Pearson

Objectives: (1) To obtain additional data on EB virus-host interactions. (2) To investigate host immune responses to tumor antigens. (3) To study the regulation of C-type virus expression in defined systems. (4) To investigate cell mediated tumor immune reaction mechanisms in vitro and in vivo.

Major Findings: EBV related research: membrane antigens, early antigens and virus capsid antigens mediated by EBV have been studied in established lymphoblastoid cell lines. Inhibitors such as mitomycin C increase the amount of antigens detected by immunofluorescence. Mouse lymphoblastoid cell hybrids have made it possible to determine whether the presence of EBV DNA is dependent on one or several chromosomes. BUDR labeled cells were super-infected with tritiated thymidine labeled virus and the heavy cell DNA was recovered and examined for associated EBV. No evidence of integrated EBV genome was found. The incubation of tumor cells with serum from patients with lipo-, fibro-, osteo-, and neuro-sarcoma inhibited the stimulation in one autologous lymphocyte-fibrosarcoma combination.

Significance to Biomedical Research and the Program of the Institute: A major effort of the Special Virus Cancer Program has been the study of the viral involvement in the etiology and course of Burkitt's tumor in man. Research on the relationship between EBV infection and the onset of Burkitt tumor, the development of EBV-coded antigens in infected cells, and the analysis of the immune response to Burkitt tumor is therefore highly relevant to total program.

Proposed Course: The contract effort will continue essentially as described above.

Date Contract Initiated: April 9, 1968

Current Annual Level: $90,000

LIFE SCIENCES, INC. (PH43-69-63)

Title: Studies on Marek's Disease as a Model for Herpesvirus Associated Oncogenesis

Contractor's Project Director: Dr. Jack Frankel

Project Officer (NCI): Dr. Gary Pearson

Objectives: The objectives of this project are (1) to determine the exact nature of the role of the herpesvirus associated with Marek's disease in the etiology of this disease, i.e. whether it is direct, or indirect (e.g. by interacting with some other agent, or by activating a covert viral oncogene-the Huebner hypothesis); (2) to establish Marek's disease as a model system for herpesvirus associated oncogenesis, using reagent grade SPF avian hosts (free of overt leukosis virus and other pathogens); and (3) to operate an avian virus testing laboratory for monitoring both hosts and viral materials used in experiments for freedom from extraneous viruses, including infectious leukosis virus.

Major Findings: In vitro interference studies were conducted with new standard pools of an avian leukosis virus (RAV-2) and cell free Marek's disease herpesvirus (MDHV). The results showed that a marked reduction in MDHV foci occurred in primary and secondary cultures of LSI-SPF CEF cells infected with RAV-2 and superinfected with MDHV. Preliminary interference studies also were performed in conventional chickens. When embryonated eggs were inoculated with RAV-2 and the chicks superinfected with MDHV by inoculation or contact with infected chicks, a marked decrease in MDHV neutralizing antibody titers occurred. In another interference test performed in vivo, deaths of LSI-SPF chickens infected with both Rous sarcoma virus (Bryan) (RSV) and MDHV were delayed three to five days as compared to chickens infected with MDHV alone. The latent period to development of the RSV-induced wing tumors was decreased by one day in groups inoculated with both viruses. Following infection of conventional chicks with MDHV, infectious MDHV could be extracted from feather follicle epithelium 11 days after infection. Viral antigen was demonstrated in feather follicle epithelium 13 days later and persisted for at least 56 days; antibodies were not detected until 49 days had elapsed. These results were in agreement with data from previous studies in which MD tumor cell suspension were used as inocula. Inoculation of LSI-SPF chicks with the GA isolate of MDHV obtained from another source, and with a passage history differing from that of the GA isolate of MDHV used in these laboratories, resulted in the same pattern of early mortality. The studies were performed in MDHV contaminated and isolator environments both with cell-free and cell-associated virus. In marked contrast to the results, no mortality occurred amongst LSI-SPF chicks housed in an isolator after inoculation with the cell associated HPRS-16 isolate of MDHV. However, MDHV was recovered from extracts of skin and feather follicle epithelium from these chickens five weeks after inoculation.

Passive immunization of LSI-SPF chicks with MDHV antiserum resulted in a marked decrease in the characteristic mortality rate induced by inoculation with MDHV. These chickens were housed in MDHV contaminated environment. On

the other hand, administration of the same antiserum and MDHV challenge to LSI-SPF chicks housed in germfree isolators did not result in any evidence of a protective effect.

Preliminary studies relating to the pathogenesis of Marek's disease in LSI-SPF chicks housed in isolators and infected with cell-free MDHV was studied by sequential changes in histopathology. The results showed a marked progressive hyperplasia of the reticuloendothelial tissues which was seen most prominently in the major lymphoid organs (thymus, bursa of Fabricius and spleen). In the terminal stages of the disease, the lymphoid tissues were completely replaced by reticular cells to the exclusion of recognizable lymphocytes. There was also a complete replacement of adult lymphocytes by reticular cells in all organs where perivascular foci of lymphocytes are usually seen.

Significance to Biomedical Research and the Program of the Institute: No satisfactory animal model is currently available for studying the exact role (i.e. whether direct or indirect) of herpes-type viruses in the induction of neoplasia. Since herpes-type viruses are associated in very high frequency with two types of human cancer, namely Burkitt's lymphoma and post-nasal carcinoma, an animal model system for developing approaches to and guiding studies on the human problem is urgently needed.

Since Marek's disease of chickens is also associated with a herpesvirus (MDHV), and this virus can now be isolated and worked with systematically in the laboratory, it seems likely that this chicken disease can be developed into the desired laboratory model.

Proposed Course: Investigations on interference and enhancement interactions between various MDHV isolates and other viruses, such as avian leukosis and other adventitious agents, both *in vitro* and *in vivo*, will be continued. The relative importance of cell mediated and humoral immunity will be investigated in experiments designed to closely follow the development and regression of Marek's disease in LSI-SPF and conventional birds.

The nature of the different responses of LSI-SPF chickens to inoculation with a variety of MDHV isolates will be investigated in terms of virology, immunology and pathology. A comprehensive study to determine the inter-relationships between virus source, dose, host, age, route of inoculation and type of chicken as related to virulence and immunocompetence will be performed.

Date Contract Initiated: November 1, 1968

Current Annual Level: $458,600

MASSACHUSETTS GENERAL HOSPITAL (NIH-71-2174)

Title: Characterization of Nucleic Acids of the Avian Myeloblastosis Virus

Contractor's Project Director: Dr. Paul C. Zamecnik

Project Officers (NCI): Dr. Timothy E. O'Connor
Dr. Robert A. Manaker

Objectives: To analyze the end groups and acromolecular sequencing of the large molecular weight RNA of avian myeloblastosis virus (AMV) and to analyze the minor base composition of the transfer RNA of AMV.

Major Findings: High molecular weight RNA was prepared from AMV to determine the nucleotide sequence of the molecule adjacent to the terminal ends. At present, only the 3'OH terminal nucleoside has been determined. Adenosine was found to be the predominant terminal residue, followed by cytidine. Uridine comprises 15% or less of the terminal residues in these experiments. The main impediment to sequencing this RNA has been the highly heterogenous character of the material as isolated. The purest preparations of 35 S material to date contain at the 3'OH end 67% adenosine and 15% cytidine. Since avian tumor viruses as well as other oncorna viruses are known to be mixtures of closely related viruses, end group studies may indicate the predominant type of virus present in a mixture, although related viral species may also have the same terminal sequence. These results are not in agreement with others who have reported the 3'OH end to be uridine.

A comparison was made of the base composition of tRNA from AMV with that from Cofal-negative chick liver and from infected myeloblast tRNA. Small but significant differences in content of major bases are present between virus and host cell tRNA. More striking differences exist in certain minor bases. In virus tRNA, lower levels of all modified pyrimidines (except pseudouridine) and levels of all methylated guanines are higher than in the host cell tRNA. AMV tRNA has all minor bases so far found in host tRNA and no evidence exists of additional bases in AMV tRNA. However, a number of minor bases have not yet been assayed by this method. The content of 3-methylcytosine in the virus is 1/5 the level in the cell. This is a rare minor base present in but 12-25% of individual host cell tRNA molecules.

Recent findings suggest that the "70 S-associated" 4 S RNA contains in addition to the 4 major bases, the minor bases: pseudouridine, dihydrouridine, and 5-methylcytosine. Other minor bases may be present. At this time it is reasonable to infer that this 4 S RNA can qualify as tRNA. Preliminary work showed adenosine to be the predominant terminal nucleoside.

Fifteen primary and secondary cultures of spleen cells from Hodgkin's patients were pulsed with ^{3}H-uridine and five cultures with ^{3}H-thymidine. Upon centrifugation of culture fluids, radioactivity occurred in the 1.16 region. Pelletized fractions from the 1.16 region were examined by electron microscopy and particles suggestive of C-type were seen.

Significance to Biomedical Research and to the Program of the Institute:

The elucidation of the nucleotide sequences of the 70 S RNA of AMV and other oncogenic RNA viruses may reveal segment active in specific functions and as binding sites of viral polymerases or inhibitors thereby increasing our knowledge of transcription processes. Elucidation of the differences in tRNA-encapsulated in virions and those present in normal and virus-infected cells may show how virus infection dominates translation as well as transcription processes. Hodgkin's disease has been suspected to be virally-induced. Recent observations suggest this may be true. An excellent opportunity exists in this laboratory to investigate viral relationships in this disease.

Proposed Course: The analysis of nucleotide sequences at terminal ends of large molecular weight tumor virus RNA will continue. A more detailed analysis of the minor bases of AMV tRNA will be conducted. The minor base constitution of the 70 S-associated 4 S RNA of AMV will be scrutinized. Pilot studies on viral associations with Hodgkin's disease will continue.

Date Contract Initiated: June 29, 1971

Current Annual Level: $95,790

MASSACHUSETTS GENERAL HOSPITAL (NIH-72-2012)

Title: Activation of Oncogenic Viruses and Induction of Cancer by Immunologic and Non-immunologic Methods

Contractor's Project Director: Dr. Paul Black

Project Officers (NCI): Dr. Adi Gazdar
Dr. Michael Chirigos

Objectives: To determine the relationships between chronic allogeneic disease, immunosuppression, and interferon inducers on the activation of covert infections by oncogenic RNA viruses.

Major Findings: The graft versus host reaction (GVHR) in vivo and its in vitro counterpart the mixed lymphocyte culture (MLC) were used in this study. Test systems were assayed for virus by the Klement XC and Bassin S+L-techniques. The test systems included: (1) Spleen cells from ($C_{57}Bl_6$ x DBA) F_1 mice (hereafter called BDF_1), either assayed directly, or cultured for 3 days in vitro. (2) Spleen cells from BDF_1 mice undergoing a GVHR (previously inoculated with DBA/2 cells), directly or cultured for 3 days in vitro. (3) Spleen cells from (BALB/c x A/J) F_1 mice (hereafter called CAF_1), as above. (4) Spleen cells from CAF_1 mice undergoing a GVHR (previously inoculated with BALB/c spleen cells, with or without mitomycin-C. (6) Spleen

cells from CAF_1, BALB/c, A/J mice cultured separately with or without phytohemagglutinin (PHS), concanavalin-A (con-A), or iododeoxyuridine (IUDR).

Cultures were tested for proliferation by the addition of 1 μCi-^{3}H-thymidine 4 hours before termination of cultures and assessed by standard liquid scintillation techniques. All cultures were coded and assayed for leukemia viruses blindly.

Activation of leukemia virus during the GVHR. Cultures of spleen cells from uninoculated CAF_1 and BALB/c mice were negative for leukemia viruses by the XC or S+L- assays, or both in 15 of 16 experiments. However, cultures of spleen cells from CAF_1 mice previously inoculated with parental BALB/c cells were positive for leukemia virus by the same assays in 10/11 experiments; titers in these cultures ranged from $10^{1.2}$ to greater than $10^{3.2}$ $TCID_{50}$ (50% tissue culture infectious doses)/ml.

In contrast to the results observed with CAF_1 cells, leukemia viruses were infrequently recoverable from BDF_1 spleen cell preparations, and in 4 of 16 allogeneic spleen cell preparations. Titers in the positive BDF_1 cultures did not exceed $10^{1.2}$ TCID 50/ml.

Activation of leukemia viruses in mixed lymphocyte cultures (MLC). Three to seven day old cultures of mixtures of BALB/c and CAF_1 spleen cells were positive for leukemia viruses by the XC or S+L- assays, or both, in 7 of 11 experiments. In three cultures which did not produce virus, lymphocyte stimulation was sub-optimal, with isotope incorporation ratios of only 2.5 x control levels, whereas the 7 positive cultures were stimulated at a minimum of 5x the control level. CAF_1 and BALB/c spleen cells cultured separately for the same periods were negative for viruses.

Relationship of phytohemagglutinin-induced blastogenesis to virus activation. Lymphocytes of CAF_1, BALB/c, or A/J mice cultured in the presence of PHS underwent marked blastogenesis but did not release virus following this treatment. Similarly, titers of leukemia virus from cultured spleen cells of CAF_1 animals undergoing a GVHR were not altered by PHA treatment ($10^{1.2}$ $TCID_{50}$ per ml with or without PHS). The proliferative response of spleen cells from CAF_1 mice with the GVHR to PHS was significantly less than that of normal CAF_1 spleen cells. Spontaneous blastogenesis in these cultures during the 1st day was 2.8 x control values, but fell below controls by day 3.

Both leukemia virus positive MLC's and leukemia virus negative PHA cultures showed proliferative responses as measured by isotope incorporation. Mitomycin-C treatment of responding BALB/c cells prevented both blastogenesis and virus release. Both BALB/c and CAF_1 lymphocytes when cultured with IUDR released leukemia viruses in preliminary trials; in addition IUDR increased the yields from MLCs.

These results would appear to be the first instance of in vitro activation of leukemia viruses by immunological techniques. Activation does not appear to be solely the result of transformation of lymphocytes because PHA induced marked blast transformation in CAF_1 lymphocytes, yet activation did not occur. Furthermore, PHS did not increase the titer of recoverable leukemia virus in lymphocytes from mice undergoing GVHR. Similarly, in vivo challenge of CAF_1 mice with sheep erythrocytes, allogeneic cells, and Freund's adjuvant did not activate leukemia viruses; studies using in vitro antigenic challenge of lymphocytes from immunized animals are in progress. A non-immunological mechanism that could activate leukemia viruses seems remote because of the failure to find virus release upon co-cultivation of CAF_1 and mitomycin-treated BALB/c spleen cells.

The biological significance of the leukemia virus activation is apparent since treatments which prevented cellular proliferation and virus activation, e.g., mitomycin-C treatment of donor cells, were also shown to prevent the GVHR and lymphoma development. In addition, none of 81 BDF_1 mice developed a lymphoma following the injection of DBA/2 spleen cells and in this combination leukemia virus was infrequently detectable in vitro or in vivo.

Activation or induction of murine leukemia virus from normal embryo cells.

Primary embryo cultures were established in routine fashion from mice of the following strains: Charles River Swiss CD[1], spf C57B1/6 MI. Various procedures were attempted to induce MuLV from these cells. The presence of virus was determined by the XC test. Virus was recovered after 2 weeks of leucine deprivation; a questionable positive XC test was obtained with the 5-week leucine deprivation samples. Attempts to induce MuLV from embryo cells following treatment with mitomycin-C have not been successful.

Significance to Biomedical Research and the Program of the Institute:

This contract contributes important new information about the relationship between immunologic abnormalities and enhanced susceptibility to oncogenesis of suspected viral origin. A better understanding between the two may be of value in the formulation of approaches to the prevention of malignancies developing in the wide range of human disease states associated with immunologic abnormalities.

Proposed Course: The studies completed strongly suggest that lymphocyte-lymphocyte interactions can activate leukemia viruses in vivo and in vitro. The relationship to lymphomas occurring in patients with autoimmune disease or transplantation reactions is obvious. The contractor will attempt to determine whether virus is activated in the donor's or the recipient's cells by labeling techniques and electron microscope localization. Studies will be continued to determine whether other treatments activate covert virus infections. Lymphocyte-fibroblast

and fibroblast-fibroblast interactions will be followed for evidence of viral activation, and further work will be carried out on the induction of mouse leukemia virus from normal embryo cells.

Date Contract Initiated: September 15, 1971

Current Annual Level: $74,370

MERCK AND COMPANY, INC. (NIH-71-2059)

Title: Oncogenic Virus Research and Vaccine Development

Contractor's Project Director: Dr. Maurice Hilleman

Project Officers (NCI): Dr. Robert A. Manaker
Mr. J. Thomas Lewin

Objectives: To conduct investigations designed to develop vaccines or other agents effective for the prophylaxis and therapy for human neoplasia of suspected viral etiology.

Major Findings: Multiple construction and renovation projects have been involved in the expansion and reorientation for this program. Remodeling of a laboratory, physically separated from the animal tumor virus area, was recently completed and is in use for Herpes simplex type 2 vaccine work. Two rooms (440 sq. ft.) in Bldg. #43 were remodeled and equipped and are in use for the germ-free derivation of kittens for the SPF cat colony breeding nucleus. Plans were completed for the renovation of half of Bldg. #65 (5,940 sq. ft.) for housing an SPF cat colony and for housing experimental cats. The construction and equipping of the new biohazard containment building #26B (12,096 sq. ft.) for laboratory work is progressing on schedule. The projected completion date is September, 1972.

Tumor-specific cellular vaccine development: The preparation and assay of tumor cell vaccines for protective efficacy in the hamster model system was continued at a lower priority level. Testing of adenovirus 31 tumor cell fractions prepared by mechanical disruption of the cells and fractionation by differential centrifugation was completed. None of the vaccines (crude cell homogenate, nuclear fraction-$\omega^2 t = 10^7$ pellet, membrane fraction-$\omega^2 t = 5 \times 10^9$ pellet, particulate fraction-$\omega^2 t = 10^{11}$ pellet, cell sap-$\omega^2 t = 10^{11}$ supernate) protected hamsters against development of tumors when they were challenged by inoculation of viable homologous tumor cells. Work on the preparation of two other types of tumor cell antigens was continued. Cell membranes were prepared from a adenovirus 12 tumor cells by hypotonic extraction and were solubilized by sonication. The solubilized material was fractionated on Sephadex G200

columns and the desired fraction concentrated by the Diaflo membrane technique. The first batch of test and control antigens is on test for protective efficacy in hamsters. Preparation of additional batches of antigen for assay is in progress. Technology is still being developed for the preparation of adenovirus 7 tumor cell membranes by flow sonication and flow zonal centrifugation.

Investigation of the host immunologic response to nonprotective tumor cell vaccines is being conducted in hamster-tumor model systems. The first series of experiments was designed to test the effect of inoculation of known nonprotective vaccines before, simultaneously with, or after immunization with a known effective vaccine (5×10^6 γ-irradiated tumor cells). Most of the experiments in this series are on test. Final results with one of the nonprotective vaccines, SV_{40} tumor cell ghosts prepared by hypertonic extraction, showed that this vaccine did not interfere with the ability of the host to reject viable homologous tumor cells after vaccination with 5×10^6 γ-irradiated SV_{40} tumor cells.

Attempts to render nonprotective SV_{40} tumor cell vaccines effective by the administration of poly I:C before, simultaneously with, or after vaccine, single or multiple doses, or by different routes were not successful in the hamster model system.

Studies on the role of fetal antigens in tumor immunology are being conducted in the SV_{40}-hamster model system. In the first series of experiment, γ-irradiated, 9-12 day gestation fetal cells of multiparous origin did not protect adult male or female hamsters against tumor development when challenged with 5000 homologous tumor cells. Experiments are in progress wherein the vaccines were prepared from primaparous 10-day gestation embryos and are being tested in the SV_{40} virus-newborn hamster model system and in the adult hamster-tumor cell challenge system with a 2500 cell challenge dose.

Virus vaccine development: This project is still in the initial stages. The work in progress is concerned primarily with basic needs such as virus propagation, virus concentration and purification, preparation of specific antisera, and establishment of routine assay procedures.

The KT (Kawakami-Theilen) strain of feline leukemia virus (FLV) was routinely propagated in roller bottle (1 liter/bottle) suspension cultures of the virus-shedding FL74c cell line. Ten liter lots of culture fluid were concentrated (1000x) and purified by flow zonal centrifugation and isopynic centrifugation on sucrose gradients. Modifications in technology are still being made to increase the purity of the concentrated virus. Virus yields of 10^{13} virus particles/ml were readily achieved.

In order to provide an adequate supply of healthy cats for future experimental work, establishment of a specific pathogen-free cat colony was proposed. The first step, the germ-free derivation of the breeding

has been in progress for two months. All eight isolators are occupied by kittens (16 females, 7 males) ranging from 1 to 8 weeks in age.

Significance to Biomedical Research and the Program of the Institute:

If viruses are an essential element in the genesis of some human cancers, prophylaxis by vaccines to prevent or minimize infection should provide a rational approach to cancer prevention. This could be accomplished by living or killed virus vaccines or possibly by vaccines of purified virion sub-units. Although greatest benefit could be derived by prevention of infections transmitted horizontally after birth, a potential benefit from vaccines may be derived where viruses are transmitted vertically but do not express their full antigenic complement. Non-oncogenic viruses may function as essential co-factors in expression of neoplasia, and immunity against such secondary agents might prevent expression of the neoplastic state. In addition, vaccination with homologous virus in a virus-dependent cancer may enhance specific humoral antibody or cellular immunity. This research project is of fundamental importance to total program.

Proposed Course: Efforts to prepare tumor-specific cellular antigens for immunoprophylaxis of cancer and to study the immunologic response to such antigens will continue. Tests with poly I:C for adjuvant effect on ineffective cellular vaccines will be completed. Work towards development of a feline leukemia-sarcoma virus vaccine and a herpesvirus type 2 vaccine will be continued as rapidly as possible. If no problems arise, the germfree derivation of kittens for the SPF cat colony should be completed in several months.

Date Contract Initiated: March 1, 1971

Current Annual Level: $1,016,000

UNIVERSITY OF NAPLES (NIH-71-2056)

Title: Studies of Non-Virion Antigens

Contractor's Project Director: Dr. Giulio Tarro

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To determine whether Herpes simplex virus-specific non-virion antigens occur in certain types of human tumors as evidence of the incorporation of viral genome in tumor cells. To search in human sera obtained from selected cancer patients for the presence of antibodies which react specifically with herpesvirus non-virion antigens.

Major Findings: To determine whether herpesvirus non-virion antigen produced early post-infection with the Schooler strain HSV-1 was strain

specific, six strains recovered from oral lesions were used to produce non-virion antigen. No non-virion antigen reactive with antibodies to the Schooler strain antigen was detected with 4 of the strains while 2 reacted positively. This antibody also did not react with a type 2 genital herpes strain. In collaboration with Dr. Ariel Hollinshead the antiserum to HSV-1 non-virion antigens was found to react with soluble cell membrane antigens extracted from lip carcinoma and from cervical carcinoma.

The contractor has shown recently that the 4 strains of HSV-1 do produce non-virion antigens because antibodies induced in guinea pigs hyper-immunized with these strains react with Schooler strain HSV-1 reference antigens. HSV-1 strains probably induce multiple antigens of the non-virion variety in different concentrations accounting for the variability in reactivity in specific systems. Antibodies have been prepared against HSV-2 non-virion antigens. These react both with HSV-2 antigens and antigens from most strains of HSV-1. Apparently the component of HSV-2 antigens engendering antibody to HSV-1 antigen is present in insufficient amount in infected cells to be detected by the antiserum to the Schooler strain HSV-1 antigens. Therefore, to establish the role of herpes-viruses in certain human tumors, many sera from patients with these tumors must be tested against these non-virion antigens, or antisera to these non-virion antigens must be tested against antigens of known potency from selected tumors, because these antigens, while capable of stimulating antibodies, may be below the limits for detection by the procedures used.

Significance to Biomedical Research and the Program of the Institute:

Certain herpesviruses have been etiologically associated with lympho-proliferative diseases in man and animals. Two other members of the herpesvirus group have been suspected to be of etiological significance in the development of the renal carcinoma of the frog and cervical carcinoma in humans. This particular contract was instituted to develop serological reagents for detecting non-virion antigens expressed early after infection of cells by herpesvirus. Such reagents would be useful for evaluating the relationship of herpesviruses to oncogenic processes in man.

Proposed Course: The contractor will examine certain types of human tumors for evidence of the presence of non-virion herpesvirus antigens and search human sera from cancer patients for antibodies that react specifically with the herpesvirus non-virion antigens.

Date Contract Initiated: April 9, 1971

Current Annual Level: $30,000

OHIO STATE UNIVERSITY (NIH-69-2233)

Title: Application of the Radioiodine Labeled Antibody Technique to Studies on Virus-induced Tumors

Contractor's Project Director: Dr. David S. Yohn

Project Officers (NCI): Dr. Jack Gruber
Dr. Virginia C. Dunkel

Objectives: To apply the paired radioiodine labeled antibody technique (PRILAT) to the detection of virus-induced tumor antigens in human tumor cells.

Major Findings: The paired radioiodine labeled antibody technique (PRILAT) has been adapted for use in serologic studies of human sera for antibodies to mammalian oncornavirus antigens. The direct PRILAT inhibition test has been used. Antibody (IgG) to ether-extracted FeLV or MSV has been labeled with ^{125}I, and normal IgG of the same animal species has been labeled with ^{131}I and mixed in equal protein concentrations. The test consisted of attempting to block the reaction of anti-FeLV or anti-MSV with formalin-acetone fixed cells known to contain oncornavirus antigens. The same sera were tested by direct complement-fixation (CF) and by CF inhibition tests using soluble antigens obtained from oncornavirus producing cell cultures. The latter tests have been used to test for antibodies to the gs-3 mammalian interspecies oncornavirus antigen. Tests conducted on over four hundred sera obtained through the SVCP have provided presumptive evidence of antibodies to oncornavirus antigens in human sera, particularly those from patients with breast carcinoma, lymphosarcoma, liposarcoma, Hodgkin's disease, rhabdomyosarcoma, reticulum cell sarcoma and acute lymphocytic leukemia.

Significance to Biomedical Research and the Program of the Institute:

This project was designed to apply PRILAT as a very sensitive tool for the detection of specific reactions between humoral antibodies and tumor cell surface antigens. Because the method permits discrimination between specific and non-specific binding of serum globulins, it is a valuable tool in the study of human tumor antigens.

Proposed Course: This contract terminates on June 26, 1972. Important aspects of the work will be incorporated into another contract.

Date Contract Initiated: June 27, 1969

Current Annual Level: $90,000

OREGON STATE UNIVERSITY (NIH-71-2175)

Title: Studies on the Replication and Function of Nucleic Acids Isolated from Oncogenic Viruses

Contractor's Project Director: Dr. George S. Beaudreau

Project Officer (NCI): Dr. Albert J. Dalton
Dr. Ursula Heine

Objectives: To study the enzymatic and biochemical changes occurring during cellular transformation by oncogenic virus and to relate these biochemical modifications to observable ultrastructural events and alterations.

Major Findings: Chick embryo cells infected with MC29 tumor virus release virions into the culture medium within 10 hours after infection. In this short period the cells must establish the necessary biochemical reactions for virus replication, and it seems that some of the heretofore inaccessible aspects of early virus infection might be examined. The contractor has chosen initially to look at the fate of the nucleic acid in the infecting virion and to look for and follow the development of the virus-specific DNA polymerase in the cell infected with tumor virus.

There is found in the virus-infected cells a DNA polymerase activity that is many-fold stimulated over that found in control cells. This enzyme has a sedimentation coefficient that appears to be slightly greater than 8 S. This may be larger than the sedimentation coefficient of the DNA polymerase as isolated from the virus (7.6 - 7.8). The enzyme appears to be associated with the outer membrane. There is little evidence for this enzyme increasing in the cell prior to release of virus. Indeed, the large accumulations are detectable 48 hours after infection.

The contractor has studied the fate of the MC29 virus RNA within the infected cell during the eclipse period of replication, when no free virus can be detected. MC29 virus, labeled with ^{3}H-uridine, was adsorbed to the cells and after short periods the cell homogenates were examined for ^{3}H-labeled virus RNA. Initial experiments have shown virus RNA in association with the polysome fraction of the infected cells.

Significance to Biomedical Research and to the Program of the Institute:

This project was undertaken as a collaborative study with investigators at NCI to determine the intracellular sites at which specific events in the very early stages of virus infection and replication occur. Such information obtained on a defined virus-host cell system under controlled conditions is important for the interpretation and significance of data acquired on other malignancies.

Proposed Course: The present approach is under evaluation. The continuation of this project will depend upon the assessment of the data acquired and possible refinements in technique.

Date Contract Initiated: June 28, 1971

Current Annual Level: $33,640

PENNSYLVANIA STATE UNIVERSITY (NIH-70-2024)

Title: Studies on the Oncogenic Potential of Defective Human Viruses

Contractor's Project Director: Dr. Fred Rapp

Project Officers (NCI): Dr. Robert A. Maraker
Dr. Jack Gruber

Objectives: To conduct a systematic study of the oncogenic potential of defective human viruses.

Major Findings: Additional cell lines were developed following exposure to HSV-2 previously inactivated with ultraviolet light. These cells were shown to be oncogenic when inoculated into newborn hamsters. A number of these cell lines have been characterized and shown to contain herpes-specific antigens in a proportion of the cells in culture. These antigens cause the production of antibodies in tumor-bearing animals that react with cytoplasmic antigens and are capable of neutralizing herpes simplex virus type 2. Thus far, no infectious viruses have been recovered from any of the tumor cell lines. In addition, no C-type virus particles have been observed nor have tests for antigens specific for such virus been detected in preliminary experiments carried out in this laboratory.

The tumors have a tendency to metastasize to the lung, liver, and kidney. The histopathology of the tumors suggests interlacing bundles of pleomorphic fibroblasts with tumors composed of poorly differentiated anaplastic sarcomatous tissue. The tumors infiltrated to the surrounding musculature but did not invade bone.

In further studies, thirteen herpes simplex virus (HSV) type 1 and type 2 isolates were tested for transforming ability of hamster embryo fibroblasts (HEF) following exposure of the viruses to ultraviolet light. Two of the new HSV-2 isolates have induced transformation of hamster cells and isolation and characterization of these cells is now in progress. Preliminary results suggest that they have similar properties to the previously described transformed cells. Attempts to detect C-type particles have been negative in 8 cell lines examined thus far.

Hamster cells transformed by chemically inactivated HSV-2 have now produced tumors when inoculated into neonatal Syrian hamsters. Cells derived from those tumors maintain the properties of the parental lines concerning resistance to infection by HSV-2 while supporting the replication of HSV-1.

Attempts to activate HSV in human cells in which the virus is latent using a variety of agents failed. Radioisotope experiments revealed that the latently infected cells contained parental virus DNA with about 5% of the input radioactivity recoverable. In addition, similar latent infection of cells from patients with xeroderma pigmentosum yielded extended latent periods in the presence of ara-C before virus began to be resynthesized after the inhibitor was removed. The overall results suggest that repair of the virus genome may be necessary as a prelude to renewed synthesis of infectious virus.

Host dependent restrictions on HSV replication appeared to be especially pronounced at 39° C. Comparison of infectious virus yields at that temperature revealed that all HSV-1 strains tested replicated in hamster cells at the higher as well as at lower temperatures. In contrast, HSV-2 strains did not replicate at 39° C in hamster cells although the virus was able to replicate in rabbit kidney cells at that temperature. These results suggest fundamental difference in the replication of HSV-1 and HSV-2.

Further experiments with EBV have yielded results that suggest that this virus is able to interact with HSV-2 in hamster cell lines non-permissive for either virus. Doubly infected cells produced HSV-2 antigens and synthesized infectious virus more effectively than cells infected only with HSV-2 (where replication was very poor). Neither EBV antigens nor infectious EBV was detected in the system. The role of EBV in enhancing the replication of HSV-2 is being further studied.

Significance to Biomedical Research and the Program of the Institute:

The neoplastic response to oncogenic virus infection is a slow process in contrast to common virally-induced diseases. This project was established to determine whether common viruses, which are defective in their capacity to induce a cytolytic cycle of reproduction, may establish a chronic infection terminating in neoplasia. This is an important aspect of Program. Current observations have shown that one virus, having been rendered defective, does induce oncogenesis in animal cells. This virus, a genital strain of herpesvirus, is particularly important, since it has been suspected to be related to the development of cervical carcinoma in humans.

Proposed Course: The present studies will be continued to further investigate in animals and human cells the relationships of defective herpesvirus type 2 to the oncogenic process observed. Emphasis will

also be given to EB virus and cytomegalovirus and to interactions between the herpes viruses.

Date Contract Initiated: October 27, 1969

Current Annual Level: $448,000

UNIVERSITY OF PENNSYLVANIA (PH43-65-1013)

Title: Research On Experimental and Natural Transmission of Bovine Leukemia

Contractor's Project Director: Dr. Robert Marshak

Project Officers (NCI): Dr. Michael A. Chirigos
Dr. Robert A. Manaker

Objectives: To investigate the possible viral etiology of bovine leukemia, attempt cell-free transmission of bovine leukemia by cell-free preparations, and investigate natural transmission of the disease through reciprocal foster nursing experiments.

Major Findings: A number of cell lines prepared from leukemic cattle have been examined for the presence of virus. Cell line NBC-13 was incubated with uridine-^{3}H. The culture fluid and a cell homogenate were subjected to low speed centrifugation followed by high speed sedimentation of supernatants. The pellets were subjected to centrifugation in a density gradient. The gradient fractions in which a peak of radioactivity was detected were found to contain particulates similar to virus of the C-type. The presence of the uridine label suggests that these particulates contain RNA. Production of these particulates in available cultures has been erratic, and sufficient material for more intensive study has not been acquired.

Gamma globulin separated from the serum of an animal in which regression of bovine leukemia occurred reacted in immunofluorescence tests with antigens in cells of the bovine leukemia cell line. Tests strongly indicate that these antigens are not the result of murine or feline virus contamination. Immunodiffusion tests also failed to detect the presence of the gs-3 interspecies antigen using antisera prepared against internal virion antigens of murine and feline leukemia viruses.

Significance to Biomedical Research and the Program of the Institute:

Epidemiological surveys suggested that bovine leukemia might be induced by a viral factor. Investigation was important to establish whether the observations of virally induced leukemia in avian and murine species was indicative of similar relationships in higher species, whether

horizontal spread of such tumor virus infections was a factor in the occurrence of disease in an animal population, whether there were close antigenic or genetic relationships between the viruses of different species, and whether bovine viruses might pose a hazard to humans. The observations made suggest that virus associations with bovine leukemia do exist. Further study is required to determine the significance of the association.

Proposed Course: Studies will continue to attempt to increase virus production in bovine leukemia cell lines to permit further characterization of the virus particulates observed. A reduction in the annual budget is under consideration.

Date Contract Initiated: June 18, 1965

Current Contract Level: $300,000 for 6 months

THE PUBLIC HEALTH RESEARCH INSTITUTE OF THE CITY OF NEW YORK, INC. (NIH-71-2129)

Title: Evaluation of Methods for Isolation of Virus from Human Neoplasia

Contractor's Project Director: Dr. Hidesaburo Hanafusa

Project Officers (NCI): Dr. Charles W. Boone
Dr. Robert A. Manaker

Objectives: (1) To apply the method successfully used for isolating oncogenic viruses from covert infections in animals to the recovery of viruses from human cancers. (2) To characterize viruses recovered from human cancers.

Major Findings: Nineteen fresh human sarcoma specimens were studied. Tissue cultures of these tumor cells were examined for the production of physically detectable particles by electron microscopy, radioactive labeling, and the assay of virus-specific enzymes. A part of the tissues was homogenized and examined for the ability to transform human embryo cells. Thus far no clear evidence for virus has been found by either physical or biological means.

Significance to Biomedical Research and the Program of the Institute:

Since the viral etiology of cancer has been demonstrated in mice, chickens, hamsters, rats, cats, and some nonhuman primates, it is unlikely that man is an exception. In this project, methods effective in recovering viruses from covert infections in leukemia and sarcoma of animals are systematically being applied to similar tumors of man.

Proposed Course: Research investigations under this contract have been underway for a relatively short time. Effort will continue as described.

Date Contract Initiated: April 27, 1971

Current Annual Level: $159,000

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER (NIH-71-2032)

Title: Studies of Tumor Viruses in Small Primates

Contractor's Project Director: Dr. Friedrich Deinhardt

Project Officers (NCI): Dr. Robert A. Manaker
Dr. Jack Gruber

Objectives: To study selected viruses and virus-induced neoplasia in small laboratory primates, especially marmosets, and to develop the marmoset as a laboratory animal for experimental use in viral oncology.

Major Findings: A simian sarcoma virus (SSV-1) isolated from a woolley monkey was studied. Tumor induction was observed in marmosets inoculated with this virus. The development of focus assay was completed. SSV-1 induced transformation of marmoset fetal lung cells (MFL) grown without agar overlay. Foci of piled up, spindle-shaped cells appeared as early as 4 days after infection, with little or no tendency toward satellite formation; final counts were made 21 days after infection. The titers of SSV-1 in unconcentrated supernatants collected from tumor cell cultures averaged 10^2 focus forming units/ml in untreated indicator cells but pretreatment of the indicator cells with 20 µg/ml of DEAE-dextran for 1 hour before infection increased the titers at least 10-fold. Indicator cells inoculated with dilutions of SSV-1 beyond the endpoint of focus induction also produced C-type virus, and challenge experiments indicated the presence of a 10- to 100-fold excess of an associated, interfering, nontransforming virus. Human embryonic lung cells (WI-38), in parallel assays with MFL, were similarly susceptible to transformation by SSV-1.

Group specific (gs) antigen was prepared in quantity in several batches, and antisera are being prepared in rabbits. Study of relationships of SSV-1 gs antigen to other gs antigens of mammalian and avian origins is near completion. Antigens and antisera were exchanged with Drs. Old and Schaefer for comparative studies.

Investigation of optimal conditions for assay of polymerase of SSV-1 is in progress. Marmoset sera for studies of inhibition of various viral polymerases was sent to Drs. Todaro and Gallo.

The RD-114 cell line from a human rhabdomyesarcoma, received recently from Dr. McAllister, was established in the laboratory. Six marmosets inoculated with viable cells or cell-free supernatants were free of tumor. Studies of the natural distribution of Herpesvirus saimiri (HVS) were continued with the following findings: Virus isolated from 11 of 13 blood samples obtained from healthy squirrel monkeys (SM). These isolates were shown to be antigenically similar if not identical to HVS. By co-cultivation with Vero cells virus was isolated from both whole blood (WB) and lymphocytes separated from WB on Ficoll-Hypaque (FH) gradients (FH-lymphocytes). Attempts failed to isolate virus from FH-cell-pellets (erythrocytes and polymorphonuclear leukocytes) or cell-free extracts of WB, FH-lymphocytes or FH-cell-pellets. The SM isolates were neutralized or reacted positively in immunofluorescence tests with anti-HVS sera but not with antisera to herpes simplex virus or Herpesvirus playrrhinae. Cotton-topped(Saguinus oedipus)and white-lipped (S. fusciollis and S. nigricollis)marmosets, experimentally infected with one isolate, developed a lymphoproliferative disease and survived 18-26 days post-inoculation. Macroscopic and microscopic features of the neoplastic disease were indistinguishable from those produced by the prototype strain of HVS.

The incidence of latent HVS infection in 2 colonies of SM were studied by isolation of HVS from blood obtained from healthy SM and by evaluation of HVS serum antibody levels by indirect fluorescent antibody methods. By co-cultivation of whole blood (WB) or peripheral lymphocytes (PL) with susceptible cells, HVS was isolated from 63 of 139 (45%) SM, but attempts failed to isolate virus from cell-free extracts of WB and PL. HVS was isolated from SM 2 months old but not from 5 younger SM. Only 30% of animals 1 year of age had HVS antibodies, whereas 100% of animals two or more years old had antibodies with peak titers of 1:128. Both of these findings suggest horizontal transmission of HVS early in life. Arrangements have been made to receive young, antibody-negative SM to study the effect of primary HVS infection.

Lymphoid cell lines established from HVS-infected marmosets were further characterized. Six lymphoid cell lines were established and have been serially propagated up to 8 months in cell culture. Four grew in suspension as single cells and clumps of cells, one cell line grew as a monolayer with many free floating cells and one line grew only as a monolayer. Infectious HVS was continually recovered from all the lymphoid cell lines by co-cultivation of the cells with susceptible indicator cells, and several months after the cultures were initiated very small amounts of infectious HVS also was recovered intermittently from supernatants of the cell lines. HVS-associated antigens were demonstrable in 0.1-1% of the cells by indirect fluorescent antibody methods. No specific chromosomal aberrations were observed in the cell lines after 7 months cultivation. Electron microscopic studies and cloning experiments with the lymphoid cell lines are in progress.

Significance to Biomedical Research and the Program of the Institute:

Restrictions in the host range of viruses require that a primate animal be available for study of human virus isolates. The marmoset is an excellent small primate for experimental purposes because twins are born frequently, this species has proven to be responsive to the oncogenic activity of viruses of lower animals and of other primates, it breeds well in captivity. The work accomplished under this contract has provided considerable information, not only on oncogenic RNA viruses, but has been contributing substantially to an understanding of the role of herpesviruses in oncogenic processes.

Proposed Course: The direction of effort described will continue. Studies will concentrate on herpesvirus induced neoplasia and will include RNA viruses isolated from lower primate and human tissues as these become available for this purpose. At present, the leukemia-associated virus of the Gibbon is under investigation preliminary to animal trials.

Date Contract Initiated: March 15, 1962

Current Annual Level: $522,880

RUTGERS UNIVERSITY (NIH-71-2077)

Title: Studies on Genetic Acquistion of Oncogenic Potential by RNA Animal Viruses

Contractor's Project Director: Dr. Robert W. Simpson

Project Officers (NCI): Dr. Michael A. Chirigos
Dr. Robert A. Manaker

Objectives: To determine whether a non-oncogenic RNA animal virus can gain tumor-producing or cell-transforming capability as a consequence of host-induced genetic modification of the viral RNA, by intracellular persistance of incomplete but functionally active viral genetic material, or by induced mutation.

Major Findings: Inactivation of candidate viruses such as vesicular stomatitis virus (VSV) by polyene antibiotics has been exploited as a method for initiating chronic infections at the genetic level. The most active antibiotic found in this system was a water-soluble methyl ester of amphoteracin B which does not degrade virions or produce detectable changes in the viral RNA. Collaborative work done with Dr. D. H. L. Bishop indicates that certain polyenes can replace nonionic detergents in in vitro RNA polymerase reaction mixtures with VSV suggesting that these antibiotics act to alter properties of the viral lipoprotein membrane of intact virions.

Newborn guinea pig heart cells originally infected with VSV inactivated by the compound ethylene iminoquinone (Bayer A 139) have been maintained in vitro for 3 months with no evidence for production of infectious virus.

Persistent infections have been established in HEp-2 carcinoma cells with host-range mutants of VSV that replicate nonpermissively in these cells.

Electron microscopic examination of normal guinea pig cell lines developed in this project has failed to reveal presence of C-type particles or other virus-like particles.

Attempts to induce immunological tolerance to VSV in neonatal guinea pigs were unsuccessful.

Significance to Biomedical Research and the Program of the Institute:

The genetic acquisition of oncogenic potential by RNA viruses is an intriguing possibility and one of great importance, since it is possible that a human cancer virus could be a member of an RNA virus group that normally causes non-oncogenic diseases in man. Although supporting evidence for this phenomenon in RNA viruses is quite scarce, some observations have suggested that ordinarily non-oncogenic viruses may have oncogenic potential. Thus, a thorough investigation of the capacity of non-oncogenic viruses to acquire genetic oncogenic potential is warrented.

Proposed Course: Emphasis will be shifted to attempts to activate latent viral genomes in cells originally exposed to chemically-modified or genetically restricted virus (VSV). Conditional lethal mutants of VSV will be examined for their pathogenesis in guinea pigs and capacity to effect immune paralysis. In vitro studies will be continued to ascertain the spectrum of viral genome expressions in cells harboring non-infectious, virus-specific, informational molecules.

Date Contract Initiated: February 15, 1971

Current Annual Level: $135,758

ST. JUDE CHILDREN'S RESEARCH HOSPITAL (NIH-71-2134)

Title: Studies on the Etiology of Selected Amphibian Tumors

Contractor's Project Director: Dr. Allan Granoff

Project Officers (NCI): Dr. Gary Pearson
Dr. Wilna Woods

Objectives: To determine the role of viruses, particularly herpes-type virus, in the etiology of renal carcinoma of Rana pipiens (Lucke' tumor)

Major Findings: The renal carcinoma of the frog appears free of herpesvirus at ambient summer temperatures. After 2 or more months at hibernating winter temperatures, herpesvirus and intracellular inclusion bodies develop in the renal tumor. The ascites fluid from hibernating tumor-bearing frogs has been found to be rich in Lucke' herpesvirus (LHV). Frog embryos inoculated with herpesvirus-containing ascites fluid develop renal carcinoma. This provides additional evidence for the tumorigenic activity of cell-free herpesvirus and another potential source of virus other than urine and tumor. The contractor's success in carrying out the "in vivo" virus tumor induction assay in his own laboratory now enables him to more easily enlarge the scope of his experiments. A number of cell systems have been tested for susceptibility to LHV using a variety of conditions, but evidence of virus infection has not been detected. Attempts to establish a transplantable Lucke' tumor have been initiated. Preliminary results indicate that more basic information on host vs graft reaction in this system is needed. In preparation for a search for virus-specific products in summer virus-free tumor cells, isotopically labeled RNA from both hibernating and summer tumors and from primary cultures of tumor cells has been prepared. Additionally, isotopically labeled DNA from several tumors has been obtained from frogs active at ambient temperatures.

Significance to Biomedical Research and the Program of the Institute:

Herpesviruses have been associated with the induction of lymphoproliferative diseases in animals and man. In this respect they resemble the RNA leukemia viruses of animals. One of the known RNA viruses, the mouse mammary tumor virus, induces carcinomas of the mammary gland. A parallel activity in regard to epithelial cell transformation is exhibited by the Lucke' virus. It is unknown whether herpesviruses mimic the oncogenic activity of RNA viruses by direct action in converting tissues of both and mesenchymal origin, or whether such activity is indirect, i.e., the herpesvirus infection activates expression of pre-existing RNA tumor virus infection. This project is important in providing for development of an experimental system for more intensive analysis of herpetic infections in neoplastic transformations.

Proposed Course: Effort will be continued to establish a virus-producing system in cell cultures. A major requirement for more intensive study is a reliable source of virus in reasonable quantities. The Lucke' virus will be more completely characterized, and antisera to the virus prepared in homologous and heterologous hosts will be tested for neutralizing capability. Such reagents will permit studies on the "rescue" of the virus from tumor cells, infectivity for different cell systems, and the detection of virus-specific antigens in virus-free cells. Viral DNA and complementary RNA will be prepared for further investigations on the virus-cell relationship. Evidence of C-type RNA viruses in tumor tissue will be sought.

Date Contract Initiated: May 13, 1971

Current Annual Level: $54,485

UNIVERSITY OF TEXAS, M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE
(PH43-65 604)

Title: Studies on the Relationship of Viruses to Neoplasia

Contractor's Project Director: Dr. Leon Dmochowski

Project Officers (NCI): Dr. Gary Pearson
Dr. Robert A. Manaker

Objectives: To pursue a systematic study of selected human patients with neoplastic disease to establish the possible significance of viruses in the etiology of their tumor.

Major Findings: Indirect immunofluorescence tests were applied to determine the reactivity of sera from cancer patients and their family members with their tumor cell antigens. Antibodies were detected in 50 percent of patients with osteosarcoma and 30 percent of their families which reacted with antigens on their own and other patients' tumor. Sera from normal donors were negative. Some of these sera reacted with antigens on cells of other types of tumor.

Osteosarcoma tissues cultured together with fresh human leukemic bone marrow appeared to undergo a morphological transformation. Supernatent fluids from these cultures induced focal areas of transformation in monolayers of cultured human embryo cells. RNA-dependent DNA polymerase activity was detected in the transformed cells but not in untransformed cells. Similar transformations were observed within co-cultures of other types of sarcomas and leukemic marrow cells. Particulates, detected in these cultures, had a buoyant density of 1.16 and 1.22 gm/cc, contained 50-70 S RNA and had reverse transcriptase activity. Cell-free supernatants from whole human embryo cells transformed in these studies could transmit transforming activity serially to fresh human embryonic cells.

Molecular hybridization studies have shown that the reverse transcriptase of SD-MSV-M (rat bone tumor virus) virions synthesizes DNA species from endogenous viral RNA which represents approximately 85-100% of the viral genome.

The nucleolar antigen in the tumor cells of some patients with melanoma fluctuates with the progression of the disease. Detection of this antigen may indicate changes in prognosis as an aid to early therapy. The antigen can now be localized by ferritin and by peroxidase labeling.

Sera of some patients with breast cancer, of their relatives, and of some normal individuals have antibodies which give cytoplasmic fluorescence with cells of mouse mammary tumors producing type B and type C virus particles. The nature of this reaction is being studied by suitable absorption experiments. About 50 percent of breast cancer patients examined had antibodies which reacted with intracellular antigens in tissues of breast cancers and fibrocystic disease. The presence of particulates in some cultured breast tumor tissue did not correlate with the immunological findings.

A cell line derived from pleural effusion cells from a 5-year-old child with Burkitt's lymphoma (American type) was established and found to produce type C particles. The cell lines, ESP-1, produces sufficient virus for study. The cells react by immunofluorescence with sera from some patients with lymphoma, leukemia, and solid tumors, as well as with sera from a very small number of normal donors. ESP-1 cells also give positive immunofluorescence reaction with sera of the family members of the child from whom the pleural effusion was derived. These cells have HLA patterns of the parents of the child from whom the cells were originally obtained. The type C virus particles from ESP-1 cells contain RNA-dependent DNA polymerase and 60-70 S RNA. Several lines of investigation indicate that the ESP-1 type C virus particles are immunologically distinct from other mammalian type C virus particles, although findings by some investigators suggest immunological relationship between ESP-1 and mouse leukemia virus. Further studies to characterize the ESP-1 virus are in progress.

Significance to Biomedical Research and the Program of the Institute:

Current program requires intensive, systematic investigations on selected human neoplasias to determine possible viral associations with the disease process. The work done on this project complements research in other laboratories and provided a major contribution to overall program.

Proposed Course: Investigations will continue to determine the significance of the transformations induced in human embryo cell cultures by fluids from combined sarcoma-leukemia cell cultures. The ESP-1 virus will be further characterized in collaboration with other laboratories within the Special Virus Cancer Program.

Date Contract Initiated: March 19, 1965

Current Funding Level: $698,700

NCI-NINDS-EMORY UNIVERSITY (NIH-NINDS-72-2301)

Title: Oncogenic Potential of Herpesviruses in Primates

Contractor's Project Director: Dr. John Sever

Project Officer (NCI): Dr. Robert A. Manaker

Objectives: To determine the possible etiological relationship of herpes simplex virus type 2 to cervical carcinoma using the Cebus monkey as an experimental animal system.

Major Findings: This project has recently been initiated. The feasibility of the Cebus monkey for experimental use for studies on cervical carcinoma has been established. Animal holding facilities are being equipped, and the necessary animals are being acquired.

Significance to Biomedical Research and the Program of the Institute:

Seroepidemiological studies suggested that the herpesvirus type 2 strains (HSV-2) infecting human genitalia might be etiologically associated with development of cervical carcinoma. Subsequent studies on UV-irradiated HSV-2 supported this possibility by demonstrating neoplastic transformation of cultured hamster cells exposed to infection. The Cebus monkey has been shown to develop vaginal lesions repeatedly upon exposure to infection by HSV-2. These lesions resemble closely those observed in infected women. This animal provides excellent opportunity to investigate the influence of HSV-2 infection in combination with the sexual activity which appears to predispose to tumor development in humans. As such, this project is most important to overall program.

Proposed Course: The project will be developed as planned. Animals will be observed for 3 years after initial infection.

Date Contract Initiated: March 1, 1972

Current Annual Level: $245,000

HÔPITAL ST. LOUIS (NIH-72-3263)

Title: Molecular Virological Studies on Human Leukemia.

Contractor's Project Director: Dr. M. Boiron

Project Officers (NCI): Dr. George Todaro
Dr. Robert A. Manaker

Objectives: To provide evidence of the presence of viral genome in human leukemic cells by biochemical methods now available.

Major Findings: This is a new contract and major findings have not yet been reported.

Significance to Biomedical Research and the Program of the Institute:

Recent data have indicated that the genome of the murine Rauscher leukemia virus contains RNA nucleotide sequences which show homology with RNA nucleotide sequences from neoplastic cell polysomes from patients with Hodgkin's disease, leukemia or sarcoma. A number of questions arise concerning the general validity of the observation, the disposition of these nucleotide sequences in polysomes of different cells of the patient, the presence or absence of a similar nucleotide sequence in the genomes of murine tumor viruses other than RLV, and the possibility that the RNA viruses may acquire such genetic information during replication in tumor tissue. Further, the significance of such genetic information relative to the transformation process remains to be determined. The clarification of issues such as these requires intensive study to which this contract is expected to contribute.

Proposed Course: The contractor will look for specific viral sequences integrated in the genome of human leukemic cells by measuring the re-association kinetics of labeled double-stranded DNA synthesized in reverse transcriptase reactions on RNA templates from various C-type mammalian viruses in the presence of unlabeled DNA from normal and leukemic cells.

Detect expression of such an integrated genome at the RNA level by fractioning leukemic cell RNA into molecular classes and checking viral specificity against the DNA synthesized in vitro on RNA templates from various C-type viruses. Structural studies of the different classes of RNA will also be made by enzymatic digestion and bidimensional electrophoresis. The template for synthetic DNA made by the action of reverse transcriptase will be extracted from Moloney Sarcoma Virus, MSV-M (MLV) grown in human cells, normal or leukemic, as well as RNA from RLV (Rauscher) and MSV-M grown in murine cells.

Look for the presence in human leukemic cells of a double-stranded RNA which, in the murine system, seems to be related to infection of cells by C-type viruses. For these biochemical studies, the cellular material

will be obtained in several ways: freshly harvested leukemic cells, leukemic cell lines, skin cells from leukemic patients, and cell lines derived from patients with "preleukemic" conditions (Down's syndrome).

Date Contract Initiated: June 28, 1972.

Current Annual Level: $94,700

UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE (NIH-72-3228)

Title: Molecular Biological Studies of Epstein-Barr Virus Infection

Contractor's Project Director: Dr. Joseph Pagano

Project Officer (NCI): Dr. Timothy O'Connor

Objectives: To determine at the molecular level the relationship between Epstein-Barr virus and host cells derived from different diseases with which infection by this virus has been associated.

Major Findings: In the short period of time this contract has been in effect, the contractor has prepared pools of purified EBV and a pool of EBV-specific complementary RNA (cRNA); established a number of cell lines and tested them for EBV genome equivalents; conducted DNA-cRNA membrane hybridization tests on biopsy specimens of Burkitt's lymphoma; and, prepared high specific activity EBV-DNA for DNA-DNA renaturation kinetics studies.

Significance to Biomedical Research and the Program of the Institute:

In order to more definitively determine whether certain herpesviruses are etiologically related to the development of some human neoplasms, it is necessary to determine whether the viral DNA is present in all the tumor cells or in surrounding tissue. The form and type of linkage between viral and cellular DNA is important to understanding differences in cellular responses to the infecting agent. Molecular biological methods to determine herpesvirus-cell interactions have not yet been intensively pursued. These studies are expected to provide more definitive information on the relationship between the infective process and neoplastic change than has been possible by the serological techniques already applied. Developments in molecular biology permitting detection of incorporated viral genetic material, perhaps even in individual cells, provides a tool for attainment of information in situations where complete virogene expression is lacking. This approach may help resolve the question whether the strong association between these viruses and tumors is a fortuitous circumstance, and the virus merely a passenger, or whether virus strain differences, or differences in the means by which the herpesvirus DNA integrates with the DNA of the host cell, are important aspects of virus-induced neoplastic change.

Proposed Course: Four broad areas of investigation will be pursued. These are: study of the integration of EBV-DNA within cultured lymphocyte lines; determination of the genetic relationships between herpesviruses, preparation of large amounts of EBV-DNA in lymphocytes; and investigation of the induction of cellular DNA synthesis by EBV.

Date Contract Initiated: April 25, 1972.

Current Annual Level: $76,960

MELOY LABORATORIES (NIH-72-2306)

Title: Collaborative Project on the Oncogenic Potential of Herpesviruses in Primates.

Contractor's Project Director: Dr. John Sever

Project Officer (NCI): Dr. Robert A. Manaker

Objectives: To maintain an animal facility to study the Cebus monkey as an experimental animal system for determining the possible etiological relationship of herpes simplex virus type 2 to cervical carcinoma.

Major Findings: This project has recently been initiated to support the NCI-NINDS-Emory University Contract NIH-NINDS-72-2301. The animal holding facilities are being equipped and the necessary animals are being acquired for the experimental studies of cervical carcinoma in the Cebus monkey.

Significance to Biomedical Research and the Program of the Institute:

Seroepidemiological studies suggested that the herpesvirus type 2 strains (HSV-2) infecting human genitalia might be etiologically associated with development of cervical carcinoma. Subsequent studies on UV-irradiated HSV-2 supported this possibility by demonstrating neoplastic transformation of cultured hamster cells exposed to infection. The Cebus monkey has been shown to develop vaginal lesions repeatedly upon exposure to infection by HSV-2. These lesions resemble closely those observed in infected women. This animal provides excellent opportunity to investigate the influence of HSV-2 infection in combination with the sexual activity which appears to predispose to tumor development in humans. As such, this project is most important to overall program.

Proposed Course: The project will be developed as planned. Animals will be observed for three years after initial infection.

Date Contract Initiated: March 30, 1972.

Current Annual Level: $150,700

Dr. Paul H. Levine, VLLB, DCCP, NCI, Chairman
Dr. Ronald B. Herberman, CTIS, LCGBY, GL&C, NCI, Vice-Chairman
Dr. Gary R. Pearson, VBB, NCI, Executive Secretary

THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE (NIH 71-2109)

Title: Anti-tumor Reactivity in Patients with Leukemia and Lymphoma

Contractor's Project Director: Dr. George W. Santos

Project Officer (NCI): Dr. Ronald B. Herberman

Objectives: To perform assays for cellular and humoral immunity against tumor-associated antigens in patients with acute leukemia and lymphoma, with an aim toward using one or more of these assays to monitor immunotherapeutic manipulations. To correlate the results of these assays with each other and with the clinical state of the patients. To search for common antigens in these tumors and to look for immunological reactivity of family members and unrelated individuals to the tumor antigens.

Major Findings: Twenty-one patients with acute leukemia, mainly acute myelogenous leukemia, and three patients with lymphoma have been studied. Only initial testing of the patients against their tumor cells has been performed thus far, because of the prolonged period of chemotherapy. Skin tests with mitomycin-treated cells have given negative results thus far. Mixed lymphocyte cultures with HL-A identical siblings have given positive results in 3 of 4 families. In the cellular cytotoxicity assay, some positive results against leukemic cells have been obtained with 2 families. The migration inhibition assay has given negative results thus far. A cytotoxic antibody has been found in the serum of a father of a patient with acute myelocytic leukemia and in the sister of two normal adults. This antibody appears to react specifically with leukemic cells.

Significance to Biomedical Research and the Program of the Institute: Clinical, epidemiological and laboratory studies suggest that acute leukemia in man is a virus induced disease. Study of immune reactions to tumor-associated antigens in patients with leukemia and their family members should be useful in evaluating the role of possible oncogenic viruses in human tumors and in providing assays for monitoring attempts at immunotherapy.

Proposed Course: Reactivity to autologous and allogeneic tumor cells will be looked for. Tests will also be performed on family members against remission cells of the patients as well as against leukemic cells. Efforts will be made to further develop the migration inhibition assay, with an emphasis toward performing a direct migration assay. The specificity of the observed antibody reactions and of the cellular reactions will be closely examined.

Date Contract Initiated: May 1, 1971.

Current Funding Level: $110,000

ROSWELL PARK MEMORIAL INSTITUTE (NIH 72-2014)

Title: Stimulation of Immunity Against Tumor by Enzymatically Treated Autologous Cells

Contractor's Project Director: Dr. James F. Holland

Project Officer (NCI): Dr. Paul Levine

Objectives: To develop a vaccine that is effective in the prevention and cure of murine leukemia and to apply these findings to the treatment of human leukemia.

Major Findings: Studies using combination chemotherapy and immunotherapy were developed indicating that neuraminadase-modified leukemia L1210 cells were effective in the treatment of murine leukemia. Groups of mice receiving cyclophosphamide, methetrexate, and BCNU were treated with a single injection of 10^7 vibrio cholera neuraminadase-modified leukemia L1210 cells intraperitoneally. Between 30 and 90 percent of mice were cured by a single dose of neuraminadase treated cells in each of these chemotherapy groups.

The findings obtained with L1210 were applied to spontaneous leukemia occurring in AKR mice. Remission was induced with Vincristine and steroids, and immunotherapy was implemented with neuraminadase treated thymocytes. Approximately 30 percent of the animals were still alive and free of residual disease at 100 days in two experiments, whereas immunization with neuraminadase-treated L1210 leukemic cells was ineffective. In addition, immunotherapy with AKR neuraminadase-treated cells without preceding chemotherapy was ineffective.

Significance to Biomedical Research and the Program of the Institute: In spite of the increasing effectiveness of chemotherapy and the treatment of acute leukemia in humans, relatively few patients have long survivals. Acute myelocytic leukemia, in particular, is a devastating disease with a poor prognosis. The use of immunotherapy to increase the length of survival provides great promise because it enables the individual to use his own host mechanisms to control the disease without the toxic effects from chemotherapy that are required to eliminate the last leukemic cell. The findings from this contract, which uses drug protocols currently in effect in humans, will be directly applicable to the control of human leukemia. The ability of this investigator to achieve better results with spontaneous AKR leukemia, a disease of known viral etiology which is associated with a poor immune response to the disease in the host, indicates that this method for management human leukemia may be successful

Proposed Course: Attention will be given to determining the specificity of the immunotherapy. A correlation between the effectiveness of cell-mediated and humoral factors in control of the disease will be pursued. The treatment protocols necessary to obtain the maximum response from immunotherapy will be evaluated.

Date Contract Initiated: September 15, 1971

Current Funding Level: $135,700

M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE (NIH 71-2178)

Title: Immunological Treatment of Human Neoplastic Disease

Contractor's Project Director: Dr. Joseph G. Sinkovics

Project Officer (NCI): Dr. Paul H. Levine

Objectives: To develop an in vitro test system for cell-mediated immunity using a standard cell line as antigen; to use this test system in a longitudinal follow-up of cancer patients and relate the in vitro findings to the clinical course; to apply the principles obtained in the in vitro studies to the immunological manipulation of the patient with the goal of improving the prognosis in these diseases.

Major Findings: In the first year of contract performance, the contractor has established a number of cell lines from tumors which have morphological and growth characteristics of tumor cells. He has improved the testing procedure and is now in a position to carefully monitor cancer patients over a period of time. Initial studies suggest that the test is able to detect tumor-associated antigens and that the evaluation of a variety of immunological factors, including cytotoxic and blocking factors in the patient's sera, can be correlated with the clinical course of the disease in most patients.

Significance to Biomedical Research in the Program of the Institute: The definition of tumor-specific antigens in human tumors provides a basis upon which to identify a human tumor virus. Studies characterizing tumor-specific antigens are important to the program of the Institute not only as an initial phase in the identification of possible human tumor viruses, but in the establishment of test systems for monitoring the patient's immunological response to tumor-associated and viral antigens. This contract is developing an in vitro test system to identify tumor-specific antigens in tissue culture lines. The cell lines will be prime candidates to investigate the possible presence of a human tumor virus and will also provide a standard reagent to use in immunotherapy of human cancer.

Proposed Course: Concentrate on the specificity of the newly developed in vitro immunity test with particular attention to human sarcomas. Continue to apply the test system in longitudinal studies of human cancer patients with a clearer definition of the operation of lymphocytes, blocking factors and unblocking factors in the patient's blood.

Date Contract Initiated: June 29, 1971.

Current Funding Level: $111,520

THE RESEARCH FOUNDATION STATE UNIVERSITY OF NEW YORK (NIH 71-2137)

Title: Application of Immunotherapy Proven Curative for Epidermal Tumors to other Types of Malignant Disease

Contractor's Project Director: Dr. Edmund Klein

Project Officer (NCI): Dr. Charles Boone

Objectives: To extend the application of skin sensitizer therapy proven curative for skin tumors to other types of cutaneous neoplasms as well as to deep-seated tumors of other organs.

Major Findings: The following patients demonstrated at least partial and frequently complete regression of their tumors following therapy with skin sensitizers: 8 of 14 patients with nodular basal cell carcinoma, 4 of 5 patients with mycosis fungoides, 3 of 4 patients with cutaneous reticulum cell sarcoma, 1 of 2 patients with multiple cutaneous and subcutaneous lesions of malignant melanoma, 1 of 2 patients with cutaneous metastases of mammary carcinoma, 1 of 2 patients with advanced carcinoma of the vulva. Collaborative studies were initiated with Dr. Robert Huebner to determine if evidence of immunity to any virus-associated antigens could be detected in patients whose tumors appear to be determined at least in part by genetic factors. In addition, collaborative studies with other SVCP investigators have been developed to compare immunity with specific tumor-associated antigens with immunity to the skin sensitizers used in therapy.

Significance to Biomedical Research and the Program of the Institute: The Principal Investigator is one of the few persons obtaining clinical cures of cancer with a type of therapy which appears to have an immunological basis. Using a technique that has proven to be successful in the field, it is possible to evaluate the mechanisms involved and apply them to other human tumors. In addition to providing data useful for the early diagnosis and treatment of cancer, this contract also provides materials from patients that are well characterized so that the unusual genetic and immunological findings can be applied to studies being carried on by other areas in the Special Virus Cancer Program.

Proposed Course: In the coming year, emphasis will be placed on the immunological mechanisms responsible for the successful therapy of cutaneous neoplasms with sensitizers. In addition, the role of genetics will be pursued in collaboration with other SVCP investigators. A correlation of the non-specific immune response with immunity to specific tumor-associated antigens will be expanded applying *in vitro* tests of cellular and humoral immunity as well as skin testing.

Date Contract Initiated: May 25, 1971.

Current Funding Level: $86,995

TRW SYSTEMS GROUP (NIH 70-2200)

Title: Viral Antigens and Anti-Viral Antibodies

Contractor's Project Director: Dr. Norman Weliky

Project Officer: Dr. Vincent W. Hollis

Objectives: To purify, separate, and characterize the antigens in known and candiate oncogenic viruses and the corresponding anti-viral antibodies.

Major Findings: A method using immunoadsorbents was developed for absorbing all detectable antibodies to mouse serum components from rabbit antiserum prepared by injecting mouse serum. The conditions for removing antilipoprotein antibodies were also determined. A study of the optimum conditions for absorbent preparation and for batch absorption indicated three things: (1) Sephadex G-200 worked better than G-50, G-25, or agarose; (2) for activation, 500 mg of cyanogen bromides per 100 mg G-200 worked better than reduced quantities of cyanogen bromide; (3) preparations made by coupling activated G-200 to mouse serum at pH11 were better than those coupled at pH10. Additional experiments established that goat and rabbit antihuman serum could be cleared of antihuman serum antibodies by an analogous procedure, using immunoadsorbents prepared with human serum and with human serum lipoprotein. The monkey anti-Rauscher plasma virus antiserum provided by the Project Officer was absorbed with immunoadsorbents and Bionetics Research Laboratories confirmed the absence of antimouse serum antibodies in the absorbed serum. HA titer to RLV was retained.

Significance to Biomedical Research and the Program of the Institute: Antigens cross-reacting with murine and feline leukemia viruses have been reported in human leukemic cells. This contract, by purifying and separating all the antigens associated with a known animal leukemia virus (Rauscher Leukemia Virus), will provide direct evidence to confirm or refute the existence of the cross-reacting viral antigens in animal and human tumors.

Proposed Course: Isolation and purification of murine viral antigens will be continued. Experiments will also be undertaken to isolate and purify EBV-associated antigens.

Date Contract Initiated: June 15, 1970

Current Funding Level: $121,464

ROBERT B. BRIGHAM HOSPITAL (NIH 71-2172)

Title: Tumor-specific Transplantation Antigens in Solid Tumors

Contractor's Project Director: Dr. John David and Dr. W.H. Churchill

Project Officer (NCI): Dr. Gary Pearson

Objectives: To search for and characterize tumor-specific antigens in human tumors using the macrophage migration inhibition assay.

Major Findings: Experiments designed to search for evidence of production of MIF by human lymphocytes stimulated by autologous tumor have been pursued. Modifications of the human MIF assay have been made to reduce the number of false negative assays. Assays have been attempted on materials from 21 patients with a variety of tumors (colon, breast, lung, lymphosarcoma, bladder) and completed in 14 instances. No evidence of MIF release in response to human tumor antigen has been obtained. The line 1 guinea pig hepatoma system has been used to develop a target cell cytotoxicity system. These cells were labelled with 3H-thymidine for 24 hours and then exposed to immune cells. The percent kill was determined by measuring the residual radioactivity after 48 hours. Specific cell kill in excess of 50 percent was measured by this method. Blocking antibody activity could not be demonstrated using serum from animals nearly moribund from line 1 tumor. Selective accumulation of basophils has been demonstrated at sites of reaction of either line 1 or line 10 tumors by specifically immunized animals. Accumulation of basophils has also been found at sites of reaction to line 1 extract in the skin of line 1 immune animals but not at sites of reaction to line 10 extract. Hypertonic KCI extracts of line 1 tumor inhibited the migration of specifically sensitized cells.

Significance to Biomedical Research and the Program of the Institute: In vitro assays for the degree of cellular immunity in human cancer patients are urgently needed so that (1) anti-tumor immune responses may be followed during the course of the disease and (2) large numbers of human tumors can be screened for tumor distinctive antigens. Successful application of the MIF, blocking antibody, and cell cytotoxicity tests in this laboratory has shown that in vitro assays of the guinea pig system can be useful in correlating cytotoxic and morphologic parameters in human studies. Extracts made by methods that were useful in human skin testing also work in KCI-macrophage migration test in guinea pigs. It is expected that improvements of the MIF assay and other tests with the same extracts will improve comparative studies in human and animal tumors. Better defined cross-reacting tumor antigens will provide leads for the morphological type of tumor that is most likely to have a virus causation.

Proposed Course: (1) To continue to use the MIF assay to look for evidence of cellular immunity in man to tumor antigens. KCI extracts of human tumors will be evaluated as one possible source of tumor antigen; (2) the mechanism of tumor cell kill in vitro will be studied in the newly developed target cell cytotoxicity system.

Date Contract Initiated: March 12, 1969.

Current Funding Level: $74,000

UNIVERSITY OF CALIFORNIA, LOS ANGELES (NIH 72-2008)

Title: Cellular and Humoral Immunity to Tumor Antigens

Contractor's Project Director: Dr. Paul Terasaki

Project Officer (NCI): Dr. Ernest J. Plata

Objectives: To establish the number of distinct tumor-specific antigens which exist in human tumors utilizing cellular and humoral immunity tests. To study the epidemiology of cellular immunity to tumor antigens. To test for humoral antibodies on cancer patients by blocking cellular immunity and direct reaction with tumor cells. To monitor the degree of cellular immunity during chemotherapy. To study the linkage of HL-A antigens to susceptibility to tumors.

Major Findings: In the first year of operation, the Takasugi-Klein technique was automated and an objective machine reading was developed. Collaborative studies with other SVCP contracts were developed which have already resulted in two manuscripts which were submitted for publication. Particular areas of importance were: (1) HL-A antigens and cancer patients: The degree of correspondence in the frequency of 25 separate HL-A antigens was remarkably similar for 1100 cancer patients, with tumors of the bladder, breast, prostate, lung, colon, and cervix, in comparison to the frequencies in normal control populations. Some differences which were significant, however, were the excess of HL-A1 and W18 (Te58) in Hodgkin's disease and of HL-A1 in cervix cancer. A higher incidence of Te66 in lung cancer was also of interest. More effort is now being made to subdivide the patients with tumors and increase the numbers of patients with rarer tumors. (2) Serum antibody studies: Sera from 288 cancer patients were first screened for HL-A antibodies by testing with lymphocytes from 80 random donors. They were then tested against a panel of tissue cultured tumor cells by a new plating inhibition test. Using this microtest, 2,459 combinations of serum and tumor cells were examined. Some 6% of the combinations tested yielded positive reactions. The specificity of the antibodies are being investigated. (3) Cellular immunity: A total of 63 cultured lines have been reacted with lymphocytes from over 1000 cancer patients in the micro cell-mediated test. Conditions of the test, particularly the amount of media was thoroughly studied. From the results obtained, lymphocyte mediated immunity appears to be only partially specific.

Significance to Biomedical Research and the Program of the Institute: This contract allows the application of findings in tumor immunology and genetics to large scale population studies. As evidence for tumor-specific antigens develops, population studies allow the identification of diseases which give an epidemiological pattern suggestive of an environmental agent. By determining the immune status of unaffected individuals and family members of cancer patients to tumor-specific antigens, it is possible to utilize epidemiology to select tumors which have the greatest (and poorest) chances of being caused by a virus. The studies on HL-A antigens are particularly significant because of the ability to separate diseases which

have a genetic predisposition from those which do not. The identification of people who are at high risk of developing cancer will allow specific actions to be taken in regard to diagnosis, prevention and treatment on a more manageable level.

Proposed Course: During the next fiscal year, the major effort will be focused on demonstrating the specificity of the immunological reactions that are occurring in the cancer patients. Specificity of the serological reactivity will also be analyzed using cytotoxicity and blocking studies. The role of genetics in human tumors will be pursued in conjunction with the immunological and epidemiological studies.

Date Contract Initiated: July 12, 1971.

Current Funding Level: $273,600

CHILDREN'S HOSPITAL OF PHILADELPHIA (PH 43-66-477)

Title: Interference and Immunoflurescence Studies with Cell Lines Derived from Leukemias and Lymphomas

Contractor's Project Director: Dr. Gertrude Henle

Project Officer (NCI): Dr. Paul Levine

Objectives: (1) To evaluate antibody patterns to EBV related antigens, i.e., the viral capsid antigens (VCA), early antigens (EA), and the D and R components of the EA complex in various EBV-associated diseases and controls. (2) To devise additional test procedures for humoral and cell mediated immune responses in EBV-associated diseases. (3) To investigate methods for improved propagation of the EB virus.

Major Findings: EBV-induced early antigens (EA) were found to be more disease-associated than the viral capsid antigen (VCA), in that patients with infectious mononucleosis (IM), Hodgkin's disease (HD), chronic lymphocytic leukemia (CLL), and Burkitt's lymphoma (BL), were more likely to have antibodies to EA even with low VCA titers. Normals generally did not have antibodies to EA, even with high VCA titers.

Exposure of Raji or RPMI-64-10 cells (free of detectable EBV-related antigens) to EBV derived from the HR1-K subline of P3J cells, led essentially only to abortive infections in invaded cells; that is, early antigens (EA) were synthesized but not viral capsid antigens (VCA). This permitted seperate determination of antibodies to EA and VCA in indirect immunofluorescence tests, using acetone-fixed cell smears of abortively infective Raji cells for anti-EA, and of EB3 (or HR1-K) cells for anti-VCA. Anti-VCA titers usually exceed anti-EA titers by several dilution steps.

In the course of examination of hundreds of sera for antibodies to the EA complex, two different patterns of immunofluorescence were observed: (1) Diffuse staining (D) of the nucleus and cytoplasm of infected cells; and (2) Restricted staining (R) of masses in the cytoplasm. The D component resisted methanol or ethanol fixation but was rapidly and completely destroyed by proteolytic enzyme treatment of acetone-fixed cell smears. The R component was denatured by methanol fixation, but was more resistant to proteolytic enzymes than D. Abortively infected Raji cells with R antigen always contained D. However, the D containing cells did not always contain R. The D antigen was found early after infection in the nucleus only. In time it was found in the cytoplasm and thus filled the whole cell. The R antigen developed entirely in the cytoplasm.

Data confirmed that there were three diseases which were regularly associated with high antibody levels to EBV-related antigens: IM, BL, and NPC. In these cases, anti-VCA titers usually persisted at nearly constant levels, whereas considerable changes in anti-R, anti-D, or both were observed frequently in the course of the disease. Approximately 80% IM and NPC patients have high anti-D titers which usually decline with cessation of the disease or when patients go into prolonged remissions. Anti-EA, particularly anti-R, has some prognostic significance in BL patients who have been successfully brought into remission by Chemotherapy. Those who maintain or develop high levels of anti-EA are more prone to have relapses than patients with no or declining titers of anti-EA. The reason why the anti-EA response is dominantly or solely of the anti-D type in some disease and of the anti-R type in other diseases is presently unexplained.

Several thousand sera are being titrated for antibodies to various EBV-related antigens from patients with Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin's disease (HD), lymphosarcoma (LSA), and several other malignant and non-malignant diseases. Results of these studies are being tabulated and complete analysis is being postponed until sufficiently large numbers of patients in each category have been examined.

Significance to Biomedical Research and the Program of the Institute:
A major effort of the SVCP has been to study EBV involvement in the etiology of human malignancies as BL and NPC. This contract characterized several EBV-related antigens and investigated their relationships with many malignant and non-malignant diseases. The identification of two EA antigens has indicated the posibility that different strains of EBV may be present or that if one strain is involved, the immune response may be of diagnostic or prognostic importance.

Proposed Course: Continuation and completion of the above studies and particular attention to development of an assay for cell-mediated immunity to EBV.

Date Contract Initiated: January 1, 1966.

Current Funding Level: $115,150

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (NIH 70-2076)

Title: Seroepidemiology Studies of Nasopharyngeal Carcinoma and Burkitt's Lymphoma

Contractor's Project Director: Dr. G. Blaudin de The

Project Officer(NCI): Dr. Robert Depue

Objectives: To determine whether there is an etiological relationship between a herpes-type virus, the Epstein-Barr Virus (EBV), and Burkitt's lymphoma; to study groups with high and low risk of nasopharyngeal carcinoma (NPC) with the aim of evaluating the possible interrelationship of genetics, environment, and viruses (especially EBV) in the etiology of NPC.

Major Findings: (1) Uganda: A five-year prospective study was initiated to investigate the status of African children relevant to EBV antibody levels prior to the development of Burkitt's lymphoma. (2) Hong Kong - Singapore: More than 7,000 blood samples have been collected from normal individuals to evaluate the distribution of EBV antibodies and HL-A patterns in groups at high and low risk for nasopharyngeal carcinoma. Analysis of a cross-sectional collection of sera from 2,096 individuals in the Hong Kong area indicate that EBV titers remain at a constant level from ages 2-30, but that after the age of 30, the proportion with titers greater than 1:160 increases in both males and females. Higher titers were found in the young Singapore population where approximately 20 percent of the pupulation between ages 19-29 had EBV titers greater than 1:160. (3) In Lyon, an attempt was made to standardize the EBV testing between Hong Kong, Singapore and Lyon. Studies performed at Lyon on a French population indicated a bio-modality of EBV titers with a gap from ages 10-40. A significant difference in antibody pattern was noticed from village to village in the French survey. Some villages had a substantial proportion of titers of 1:10 or below, whereas other villages had virtually no individuals with low titers. A soluble antigen from Pope's QIMR-WIL line derived from a leukemic patient reacted in high titer with NPC sera but not with BL sera.

Significance to Biomedical Research and the Program of the Institute: High EBV-antibody titers have been associated with nasopharyngeal carcinoma and Burkitt's lymphoma, but an etiological relationship has not been established. The prospective study initiated in Uganda should be able to

detect whether Burkitt's lymphoma is the result of a new infection with EB virus in an older child who has somehow managed to escape infection with EBV at an early age, and it should also be able to test an alternative hypothesis that Burkitt's lymphoma requires persistant reinfection with EBV in order to develop. The Far Eastern studies will be able to concentrate on a multi-factorial analysis of possible etiological co-factors in the etiology of a tumor with clear population clustering. The correlation of data resulting from the HL-A typing, EBV studies, and case control studies could identify factors involved in the etiology of this disease. The serological findings of higher titers in the older Hong Kong population indicated that active reinfection with EBV occurs in an area where there is a high incidence of NPC, and is therefore in support of the reinfection theory of EBV oncogenicity. The findings of EBV antibody differences by city in France are important because of the time-space clustering and drifting of Burkitt's lymphoma. Geographical variation in EBV status in consistant with the hypothesis that EBV causes Burkitt's lymphoma. The findings of a soluble antigen that differentiates between sera with Burkitt's lymphoma and nasopharyngeal is one of two important tests that are able to distinguish between high EBV-associated antibody levels, the other being the finding of the diffuse type of early antigen in NPC by the Henles while the restricted is more often found in Burkitt's lymphoma.

Proposed Course: Continued collection of data and materials in the Hong Kong, Singapore and Uganda areas will be pursued as above. Standardization of the EBV test will be assisted by cooperation between standardization laboratories in Lyon and the United States.

Date Contract Initiated: January 1, 1971.

Current Funding Level: $523,615

CENTER FOR DISEASE CONTROL (VCL-42)

Title: Etiologic Studies of Leukemia and Related Diseases Occurring in Unusual Epidemiologic or Genetic Situations.

Contractor's Project Director: Dr. Clark W. Heath, Jr.

Project Officer (NCI): Dr. Adi F. Gazdar

Objectives: (1) To perform epidemiologic and virologic studies of leukemia and related illnesses (cancer, congenital defects) occurring in unusual epidemiologic or genetic circumstances. (2) To maintain leukemia case surveillance programs in selected population areas in the United States.

Major Findings: Out of approximately 100 cases of leukemia and lymphoma brought to the attention of the CDC, 41 cases associated with unusual circumstances were selected for epidemiologic and laboratory study. The studied cases consisted of 24 community clusters, 10 multiple case families, 5 human-animal case associations, and 2 instances of marital leukemia/lymphoma.

A total of 35 cell lines from leukemia/lymphoma cases have been permanently established, screened by electron microscopy, tested for the presence of oncogenic and non-oncogenic viruses, immunoglobulin production and mycoplasma contamination by various techniques and preserved in liquid nitrogen. In the past year, 60 specimens have been collected for cell culture work, and about 150 serum specimens have been obtained, aliquoted and stored.

Thirteen cell lines derived from patients have been cross-tested for FA reactivity against the donor's serum and 2 cell lines were also tested against sera collected from relatives and contacts, with negative results.

Cell cultures, mostly from multiple case family situations have been supplied to several investigators in the SVCP. Eighteen cell cultures have been tested at the NCI for reverse transcriptase activity, with negative results.

Significance to Biomedical Research and the Program of the Institute: This contract deals with epidemiologic and genetic studies on cases of human leukemia and attempts to ascertain and clarify the etiology of human luekemia through intensive investigations of selected cases. Since clustering and genetic defects are associated with the easier detection of virus in animal systems, this contract provides specimens of particular importance to SVCP investigators because of the greater chance of identifying a human tumor virus.

Proposed Course: The contractor will continue to identify and study cases of particular interest to SVCP. In addition, a program for a systematic evaluation of the relationship between infectious mononucleosis and lymphoma will be developed.

Date Contract Initiated: July 1, 1967.

Current Funding Level: $150,000

THE UNIVERSITY OF MINNESOTA (NIH 69-2061)

Title: Tumor specific Transplantation Antigens in Solid Tumors: Evaluation of the Immune Response

Contractor's Project Director: Dr. Charles R. McKhann

Project Officer: Dr. Ronald B. Herberman

Objectives: To study events in the immune response to tumor antigens by assays for lymphocyte stimulation, cytotoxicity by immune cells, blocking antibody, and cytotoxic antibody. To study the effect of clinical state on the immune response. To perform studies on immunological manipulation of experimental tumors.

Major Findings: A heterologous antiserum to mouse plasma cells has been developed. This serum suppressed formation of antibody to sheep erythrocytes. It was found to have some inhibitory effects upon the growth of transplantable mouse tumors.

Lymph nodes of tumor bearing mice were found to produce larger amounts of immunoglobulin than those of control mice.

A serial study of cellular immune reactivity of patients to tumor-associated antigens is now in progress.

Significance to Biomedical Research and the Program of the Institute: Study of immune reactions to tumor-associated antigens on human tumors is an important part of the AVCP. Studies of immunological manipulation in animal model systems may provide information leading to successful immunotherapy in man.

Proposed Course: (1) Continue studies on inhibition of antibodies to tumor antigens by the anti-plasma cell serum. (2) Continue serial study of immune reactivity in patients.

Date Contract Initiated: April 14, 1969.

Current Funding Level: $130,011

CHILDREN'S HOSPITAL OF THE DISTRICT OF COLUMBIA (NIH 72-2071)

Title: Immunologic Reactivity of Pediatric Cancer Patients

Contractor's Project Director: Dr. Sanford Leiken

Project Officer (NCI): Dr. Edward Leonard

Objectives: To determine if children with cancer react immunologically to autologous neoplastic cells and to serve as a resource of tumor tissue from children with neuroblastoma, rhadomyosarcoma, Wilms tumor and hepatoma.

Major Findings: This is a newly funded contract and there are no findings to be reported.

Significance to Biomedical Research and the Program of the Institute: The Special Virus Cancer Program has been concerned with the problem of whether or not cancer patients possess specific tumor immunity. Evidence has been obtained by others using in vitro tests that neuroblastomas from different patients share tumor antigens. Clinical immunological and epidemiological studies indicate that neuroblastoma may be a tumor of viral origin. This contract represents the first attempts to verify in vivo antigenic relationships among neuroblastomas from different patients. Tests for cellular immunity using skin testing and in vitro techniques, when combined with virological and biochemical tests, will be of great importance to studies on the viral etiology of neuroblastoma. In addition, if reactivity is detected it may be possible in the near future to increase the immune response by the patients to the point where an adverse effect on the tumor and accompanying beneficial effect for the patient would be obtained.

Proposed Course: The contractor will concentrate on preparation of tumor cell antigens for studies which will include: (1) measurement of in vivo delayed cutaneous hypersensitivity reactions to antigen preparations; and (2) in vitro lymphocyte transformation and colony inhibition tests.

Date Contract Initiated: February 1, 1972.

Current Funding Level: $70,000

GEORGE WASHINGTON UNIVERSITY (NIH 72-3251)

Title: Clinical Tests for Immune Responses to Separate Soluble Membrane Antigens Which Appear to be Tumor-Specific

Contractor's Project Director: Dr. T. Crandall Alford

Project Officer (NCI): Dr. Ronald Herberman

Objectives: To study the immunological reactivity of tumor patients to antigens on their neoplastic cells by skin testing and other in vitro methods and to correlate these results with the clinical course of the disease.

Major Findings: This is a newly funded contract and there are no findings to be reported.

Significance to Biomedical Research and the Program of the Institute: The potential findings of common antigenicity of tumors would provide strong indirect evidence for viral etiology. This contract should: (1) allow the study of several immunological parameters in patients with neoplastic diseases; (2) provide information on the immunogenicity of soluble antigens and their potential usefulness in immunotherapy; (3) contribute information regarding common antigens in tumors of different individuals with the same disease; (4) provide materials for a correlation of tumor-associated antigens with biochemical and virological searches for a human tumor virus.

Proposed Course: The contractor will test soluble extracts from tumors and selected patients will be inoculated with these extracts to determine if the tumor specific antigens are immunogenic. Materials from these patients will be studied in collaboration with biochemists and virologists within SVCP.

Date Contract Initiated: April 1972

Current Annual Level: $84,955

ATOMIC ENERGY COMMISSION, OAK RIDGE NATIONAL LABORATORY (FS-7)

Title: Biophysical Instrumentation Development and Cancer Anatomy Program

Contractor's Project Director: Dr. Norman G. Anderson

Project Officer (NCI): Dr. Charles W. Boone

Assistant Project Officers (NCI): Dr. Robert A. Manaker
Dr. Timothy O'Connor

Objectives:

1. To investigate the immune reaction to cancer and to develop rapid monitoring assays for this purpose.

2. To determine the re-expression of fetal, embryonic, or placental antigen or isozymes in tumors, and to develop reagents and immunological tools for early cancer detection and therapy based on these antigens.

Major Findings:

1. Demonstration of circulating antibodies cytotoxic to SV40 hamster tumor cells after immunization with human embryonic cells.

2. Development of methods for isolating tumor antigens from tumor cells in tissue culture.

3. Establishment of a screening laboratory for screening human sera for fetal isozymes, antigens and low molecular weight indicator substances.

4. Modification of a cytofluorograph for direct computer data processing.

5. Development of interim fluorescence standards for quantitation of fluorescent binding to cells.

6. Discovery that a large fraction of the circulating anti-Burkitt cell antibodies in convalescent Burkitt patients and in infectious mononucleosis are absorbed out by fetal cells, and that they will also bind to SV40 transformed hamster cells, providing strong support for the concept that many of the antigens appearing in tumors, including human ones, are re-expressed embryonic components.

7. A symposium and workshop on Fetal and Embryonic Antigens in Cancer was held in Oak Ridge in May 1971 and will appear in December of this year. A second one was held in February 1972. Arrangements for rapid publication have been completed.

8. Heavy emphasis is being placed on the characterization of so-called "blocking" components in the serum of cancer patients and tumor-bearing animals.

Significance to Biomedical Research and the Program of the Institute: The development of better methods for characterizing immunological response to cancer and for detecting tumor antigens are closely associated with the elucidation of the viral causation of cancer in man. In the event a human cancer virus is authenticated, immunological methods and concepts now being used to detect cancer viruses will be used diagnostically and to monitor therapy.

Proposed Course: This contract will continue to operate in two research areas: 1) the development of better instrumental methods for detecting cancer antigens and 2) the elucidation of fetal antigens to cancer antigens.

Date Contract Initiated: July 1, 1962.

Current Contract Level: $650,000.

NEW YORK MEDICAL COLLEGE (NIH 72-3289)

Title: Immunological Responses of Breast Cancer Patients Against Autologous Breast Cancer Tissues

Contractor's Project Director: Dr. Maurice M. Black

Project Officer (NCI): Dr. Paul Levine

Objectives: To evaluate the Rebuck skin window technique as a means of identifying specific immune responses to breast tumor antigens.

Major Findings: This is a newly funded contract and there are no findings to be reported.

Significance to Biomedical Research and the Program of the Institute: Epidemiological, virological, and animal studies indicate that breast cancer is one of the most likely forms of human cancer to be caused by virus. One of the major goals of the SVCP is to provide information on the etiology and control of virus induced neoplasms. This contract will study the immune response to breast cancer antigens in humans and the information that is obtained will relate directly to the SVCP's efforts in this area.

Proposed Course: The investigator will compare pathological evidence of immune reactivity in breast cancer patients with in vivo and in vitro tests performed on the same patients and supply clinical information and laboratory specimens to other investigators in the field of breast cancer.

Date Contract Initiated: June 26, 1972

Current Funding Level: $86,010

UNIVERSITY OF TEXAS (NIH 72-3262)

Title: Human Immunity and Immune Response to the Rauscher Leukemia Virus

Contractor's Project Director: Dr. Evan M. Hersh

Project Officer (NCI): Dr. Paul Levine

Objectives: To establish the kinetics of the human immune response to Rauscher leukemia virus and to determine the ability of man to mount a primary or secondary immune response to the virus.

Major Findings: This is a newly funded contract and there are no findings to be reported.

Significance to Biomedical Research and the Program of the Institute: The fundamental premise upon which this work is proposed is that known murine leukemia viruses and a hypothetical human leukemia virus may share at least one common antigen. Evidence from a number of laboratories using immunofluorescence techniques has suggested a cross-reactivity between Rauscher leukemia virus and antigens in human leukemia cells. The materials and information provided from patients in these studies may provide important reagents for establishing tests to detect the etiological agent for human leukemia.

Proposed Course: The contractor will inoculate selected cancer patients with a formalin-killed high titer Rauscher virus preparation which has been demonstrated to be non-cytotoxic, non infectious, and non-oncogenic. Humoral antibody response and cellular immunity will be measured by a variety of *in vitro* tests in collaboration with SVCP investigators.

Date Contract Initiated: May 24, 1972.

Current Funding Level: $102,058

MAKERERE UNIVERSITY (PH43-67-47)

Title: Epidemiologic Study of Burkitt's Lymphoma

Contractor's Project Director: Dr. George Kafuko

Project Officer (NCI): Dr. Robert H. Depue, Jr.

Objectives: The overall objective was to conduct studies on the natural history, occurrence, and transmission of Burkitt's lymphoma (BL), with special reference to the etiologic role of Epstein-Barr virus (EBV). Since malaria has been considered as a contributing factor in the etiology of BL, the following specific objective has been a target during the current contract year:

> To study the relationship between malaria and BL; to investigate the immunological effects of malaria in the susceptible childhood population of the West Nile District, and to ascertain whether patients with BL have normal immune response to malaria as compared with a well-selected control population.

Major Findings: Since the malaria investigations are supplementary to the seroepidemiology survey, the pace of work was geared to that of the main project. From 1 August 1971 to 7 February 1972, the administrative set up at Arua was organized, laboratory facilities were established in the East African Virus Research Institute Field Station at Arua, and supplies, stores, equipment and apparatus were delivered there. Staff were recruited and trained. Much time was also spent in establishing good public relations with the administrative authorities and the general public in the District, so as to enlist full participation and cooperation

of all concerned. Parishes in the counties of Maracha, Aringa, Terego, Madi, and Koboko, were also selected, on the basis of population density. A parish is the smallest administrative division of a district.

For comparison and assessment of malaria endemicity in children aged 0-5 years, malariometric surveys were carried out in 7 selected parishes in the counties of Aringa, Maracha, Terego, and Madi. Assessment of malaria endemicity was made by parasite and spleen surveys. From each child examined, a thick and thin blood smear was taken on the same slide, and these were stained and examined at the Field Station Laboratory in Aura. The parasite density index has been calculated by multiplying the frequencies of parasite counts obtained for each class by the class number, adding all the products, and dividing the total by the number of positive slides. The total number of slides taken were 3120 of which 2440 were positive (78.2%). The number of children examined for spleen enlargement was 1099. The total number of enlarged spleens found was 480 (43.7%). The average enlarged spleen was 1.5. The level of malaria fluctuated between holoendemic in Obi parish and hyperendemic in Aupi, Olivu, Orinzi and Tara parishes. The parasite rates were highest in the 3-5 year age group. This is a very important observation because the peak-age incidence of BL corresponds with this same age group; therefore, this finding strongly supports the correlation observed between malaria and BL by Kafuko and Burkitt, 1970 (Intern. J. Cancer, 6, 1-9).

In Aupi parish during February and March 1972, the parasite density index was highest in the age group 0-4 years, likewise corresponding to that of BL. Malaria infection in all areas is predominantly due to P. falciparum, with P. malariae playing a secondary role. Infections due to P. ovale were less than 1%. No P. vivax. was detected. Malariometric follow-ups will involve 1500 children selected for rebleeding at 6 monthly intervals. Commencing August 1972, 20 clusters of 75 children will be investigated for rebleeding and Malariometric follow-up surveys.

Significance to Biomedical Research and the Program of the Institute: Many studies are being undertaken of EBV because of its implication in the etiology of infectious mononucleosis and its suspected relationship with other human cancers. Determining the etiology of BL is one of the most important goals of the Special Virus Cancer Program, because of the probable viral causation or association and the probability of etiological co-factors. If the etiology of BL is solved, then it is highly probable that it will have considerable application to other human neoplasms.

Proposed Course: This project will cooperate in the sero-epidemiological study of EBV in the West Nile District during the next contract year and continue studies on chronic malaria and its resultant immunological aspects in relation to BL. Malaria antibody and immunoglobulin tests will be carried out on sera from BL patients and controls, including long-term BL survivors.

Date Contract Initiated: September 26, 1966.

Current Funding Level: $26,000.

New contracts were initiated in the last five months of the year with D.C. Children's Hospital in Washington, D.C., George Washington University Medical Center, New York Medical College, and the University of Texas. These contracts will employ *in vivo* and *in vitro* immunologic tests to characterize the immune response to a variety of viral and tumor-associated antigens.

PROGRAM MANAGEMENT SEGMENT

Dr. J. B. Moloney, ASDVO, DCCP, NCI, Chairman
Dr. Louis R. Sibal, OASDVO, DCCP, NCI, Executive Secretary

UNIVERSITY OF NORTH DAKOTA (PH43-66-8) GRAND FORKS, NORTH DAKOTA

Title: Quantitative Studies on the Transmission of Feline Oncogenic RNA Viruses and Selected Herpesviruses by Certain Bloodsucking Arthropods

Contractor's Project Director: Dr. Robert G. Fischer

Project Officer (NCI): Dr. George J. Burton

Objectives: To determine whether certain oncogenic viruses can be transmitted from infected animals to healthy susceptible animals by bloodsucking arthropods. Specific objectives are: (1) To determine virus levels in arthropods which have fed on experimentally infected donor animals of known titer. (2) To determine whether the disease caused by each oncogenic virus can be transmitted biologically, i.e. by transfer of the virus via the salivary glands of the infected arthropod. (3) To determine the quantitative distribution of the virus among various organs and tissues in those arthropods demonstrating suitably high virus levels. (4) To determine whether the disease caused by each virus can be transmitted mechanically through interrupted feeding, or by transfer of the virus on the legs and body of the arthropod.

Major Findings: (a) Friend leukemia virus (FLV).

In collaboration with Drs. W. Turner and G. Burton, N.I.H., the X-C test was used to determine whether the Friend leukemia virus (FLV) complex ingested by the stable fly is altered in such a way that subsequent introduction of this insect-virus mixture into an animal system results in splenomegaly without splenic foci. The findings are consistent with the hypothesis that a "helper" activity (LLV) may be degraded more rapidly than SFFV. A low percentage of flies are capable of supporting SFFV plus helper activity for at least 14 days. An investigation to determine possible SFFV and/or helper virus (LLV?) activity in the stable fly following a single FLV meal was conducted. A study with Dr. R. Steeves, Roswell Park Memorial Institute, indicated a gradual loss of both SFFV and helper viruses. FLV infection rate studies have been conducted in other fly and mosquito species. It was found that 90-95% of the mosquitoes tested had each ingested enough FLV to infect one weanling BALB/c mouse.

(b) Feline leukemia virus (FeLV) and Feline Sarcoma virus (FSV): No virus particles have been observed in various organs of cat fleas or mosquitoes which fed on the FeLV- or FSV-infected donor cats. The fate of FSV in the cat flea, fed successive infective meals, is currently being evaluated.

(c) Herpes saimiri virus (HVS): Arthropod transmission of Herpesvirus saimiri (HVS) which induces reticulum cell sarcoma in marmosets has been investigated with the collaboration of Dr. F. Deinhardt, Presbyterian-St.

Luke's Medical Center, Chicago, and Dr. G. Burton, N.I.H. They included initial extrinsic incubation studies of HVS in relation to the yellow fever mosquito, Aedes aegypti; the malaria mosquito, Anopheles quadrimaculatus; the cat flea, Ctenocephalides felis; and the stable fly, Stomoxys calcitrans. HVS was only isolated from the midgut of Aedes and Anopheles mosquitoes, cat fleas, and stable flies up to 6 hrs. In an investigation of the possibility of transmission from an HVS-infected marmoset to a susceptible recipient during interrupted feeding activity of the stable fly, four of the six marmosets showed no apparent signs of disease after one year.

(d) Marek's disease virus (MDV): Marek's disease transmission studies are being conducted with the collaboration of Drs. J. Frankel of Life Sciences Inc., and Dr. G. Burton, N.I.H. During this first triannual period, an interrupted feeding-natural association experiment was conducted. Stable flies, Aedes mosquitoes, and triatomid bugs were allowed to partially feed on two MDV infected chickens. One hour later, the insects were allowed to complete feeding on varying numbers of both one-day-old L.S.I. and conventional Wallace chicks. No positive transmissions have occurred to date.

(e) Murine cytomegalo virus (CMV) (Henson strain). This cytomegalovirus has been supplied by Dr. D. Henson of N.I.H. Results of three experiments with stable flies indicate that CMV is viable in this insect for at least 3-4 days.

Significance to Biomedical Research and the Program of the Institute:

Viruses, which are obligate parasites, may be transferred biologically or mechanically by arthropod vectors. Mosquitoes, biting flies, fleas, ticks, and mites may suck blood from both man and domestic animals (including birds) closely associated with man. It is, therefore, important to investigate whether oncogenic viruses present in infected animals can be transferred to man. If such a vector is found, measures can be taken to control or prevent contact between the vector and human or animal hosts.

Proposed Course:

(1) Since the Herpesvirus saimiri appears to have no viability in the yellow fever mosquito, malaria mosquito, cat flea, and stable fly beyond 6 1/2 hours, only interrupted feeding transmission experiments will be pursued next year. (2) Insect transmission experiments will be continued using Marek's disease virus, murine cytomegalovirus (Henson strain), and feline oncogenic viruses, with mosquitoes, flies, fleas, and other arthropods. (3) Additional species of mosquitoes, flies and fleas will be used as test insects in these transmission experiments.

Date Contract Initiated: October 27, 1965

Current Contract Level: $25,000 (It is planned to terminate this contract after Dec. 31, 1972, since all objectives will probably have been met by then.)

UNIVERSITY OF MIAMI SCHOOL OF MEDICINE (PH43-67-1187) CORAL GABLES, FLORIDA

Title: Immunization Studies on Avian Leukosis and Related Problems

Contractor's Project Director: Dr. M. Michael Sigel

Project Officer (NCI): Dr. Gary Pearson

Objectives: (1) Measurement of the duration of immunity induced by live virus; (2) Further assessment of the specificity of protection induced by immunization with live virus; (3) Search for humoral factors other than neutralizing antibodies; and (4) Investigations of the several parameters of cell-mediated immunity.

Major Findings: (1) Their initial observations on protection against Rous tumor induction were extended to include various combinations of immunizing and challenge viruses of subgroups A, B, and C of the avian leukosis-sarcoma complex. It was demonstrated that protection against tumor induction by viruses of all 3 subgroups (A, B, C) could be achieved by immunization with a single line leukosis virus of any of the 3 subgroups. Furthermore, this protection was independent of humoral antiviral neutralizing antibody. Taken as a whole, their work seems to provide an indirect demonstration of a TSTA or VISA on the natural host system for avian leukosis and sarcoma viruses. (2) The duration of protection elicited by RAV-1 immunization was at least 9 months. (3) Immunization of chickens 2 weeks of age afforded better protection against a challenge dose RSV(RAV-1) than immunization of 14 week old chickens. (4) Inactivated virus (B-propriolactance and formalin) failed to elicit protection against RSV(RAV-1). Utilizing the *in vitro* blastogenic reaction, it was found that leucocytes sensitized to virus of one subgroup were also responsive to antigen(s) associated with another subgroup. The development of the blastogenic response began slowly and reached its peak 4-6 weeks after immunization which coincided with the period necessary for immunity to tumor induction to develop in immunized birds. (5) Soluble virus-induced surface antigen (VISA) was prepared from SR-RSV transformed hamster cells (MSR-5) by the method of Mann *et al*. The soluble extract was capable of blocking the serum mediated cytotoxic reaction against both allogeneic (clone-2) and syngeneic (MSR-5)SR-RSV transformed hamster cells. Preliminary attempts to prepare soluble RSV induced surface antigen using a KCL solubilization procedure have been started in order to determine the most suitable and efficient method for isolation of VISA.

Significance to Biomedical Research and the Program of the Institute: The overall goal of the SVCP is the control of cancer. From the immunological viewpoint, it would be extremely important to clarify the issue as to the possible existence of a transplantation antigen and its role in the disease process. Basic studies are also needed on immunity in chickens in order to understand fully the immunological implications in avian tumors, and possible application to mammals.

Proposed Course: (1) Experiments on immunization of Japanese quail, which

are free of endogenous gs antigen and helper factor, are now underway. (2) Attempts to achieve protection against sarcoma viruses in chickens and quail through immunization with a subgroup E virus are planned. (3) A further effort to immunize with a killed virus preparation, using hydroxylamine-inactivated virus is also planned. (4) Major emphasis will be placed on further work with the putative VISA isolated from RSV transformed tumor cells and on the relative blastogenic potential of chicken lymphocytes from immunized birds as correlated with tumor immunity.

Date Contract Initiated: June 23, 1967

Current Funding Level: $121,000

UNIVERSITY OF WASHINGTON (NIH-NCI-72-2037) SEATTLE, WASHINGTON

Title: Immunological and Transplantation Studies on Dogs with Cancer for Detection of an Oncogenic Virus-Carrier State

Contractor's Project Director: Dr. Rainer Storb

Project Officer: Dr. Gary Pearson

Objectives: (1) To set up procedures for studies of immune competence in dogs with lymphosarcoma and other tumors before, during, and after treatment; (2) To monitor closely those dogs undergoing relapse for biochemical or other expression of an oncogenic virus; (3) To set up immunological assays for investigation of tumor-specific antigens of canine tumors; (4) To carry out allogeneic marrow grafts in dogs with tumors as a means of preventing recurrence of leukemia.

Major Findings: This contract was awarded November 1, 1971. Because of delays in the delivery of some equipment that was vital for the initiation of the work, progress has been hampered. However, they have succeeded in starting some experiments with (a) 5 dogs with lymphomas, (b) 1 with Waldenstrom's disease, and (c) 4 dogs with other malignant tumors. Three types of studies have been carried out in dogs with lymphoma or Waldenstrom's disease: (1) One of two normal dogs was given lymphosarcoma cells immediately after irradiation. Both dogs were then infused with previously stored autologous bone marrow followed by methotrexate therapy. A dramatic increase in the concentration of DNA polymerase containing particulates in the plasma of the recipient dog that was given lymphosarcoma cells before irradiation was noted confirming previous findings. (2) One tumor dog was given 1200R of total body irradiation followed by infusion of phenotypically histocompatible marrow from a normal donor dog and post-grafting treatment with methotrexate. A dramatic regression of all tumor-bearing lymph nodes occurred within a few days following irradiation. This dog is now in apparent complete remission with a successful hemapoietic graft 55 days after the transplant. (3) One dog has been subjected to total body irradiation followed by infusion of previously stored autologous bone marrow in order to evaluate the effects of total body irradiation alone on the treatment of lymphoma. Two dogs with

other malignant tumors were given total body irradiation followed by infusion with either phenotypically histocompatible marrow from a normal dog or autologous marrow. The hemapoietic grafts were successful in both dogs and some tumor regression was noted.

Significance to Biomedical Research and the Program of the Institute: The major goal of the SVCP is the prevention or control of human neoplasia. The projected immunotherapy is aimed at providing the clinician with an additional modality of therapy which might eradicate those tumor cells which for one reason or another survive chemotherapy. Another goal of this project is to attempt to determine whether tumor-specific antigens exist in canine neoplasms. If specific transplantation antigens are detected and prove to be cross-reactive, indirect evidence will then be available for the viral etiology of canine lymphosarcoma.

Proposed Course: Until the arrival of the dog cages necessary for the in vivo investigations, efforts will be directed to establishing the necessary in vitro laboratory tests for searching for tumor-specific antigens on canine tumor cells. When the cages become available, the biochemical studies on the significance and nature of the DNA polymerase containing particulates found in the plasma of irradiated dogs will be continued. Investigations on the immunotherapeutic effects of bone marrow grafts will also be continued.

Date Contract Initiated: November 1, 1971

Current Funding Level: $160,000

UNIVERSITY OF MIAMI SCHOOL OF MEDICINE (NIH-70-2211) MIAMI, FLORIDA

Title: Studies of the Rat Mammary Tumor Derived Virus (RMTDV or BV)

Contractor's Project Director: Dr. Victor V. Bergs

Project Officer (NCI): Dr. Michael A. Chirigos

Objectives: (1) To determine whether purified C-type particle preparations of RMTDV will induce leukemia or other malignancies when administered to conventional and germ-free rats under natural and immunologically altered conditions of the host; and (2) comparative studies of the biochemical and biological properties of rat C-type viruses (BV-1, R-35, and WF-1) of different origin.

Major Findings: Studies in collaboration with NCI staff have thus far revealed that the C-type virus, which emerged spontaneously in a 2-year old line of "normal" W/FU rat embryo cells (WF-1 virus), is antigenically related to the rat C-type viruses (BV-1 & R-35) isolated from rat mammary tumors. The WF-1 virus produces cell alterations in REL cultures. It does not exhibit characteristics common to murine C-type viruses (gs-1 & gs-3 antigens, and the XC reaction).

From purification studies of the BV-1 and WF-1, diaflo ultrafiltration,

centrifugation in discontinuous and continuous sucrose gradient, it was found that the virus was distributed in 2 peaks with average densities of 1.16 and 1.20 gm/cm^3, respectively. Infectivity studies showed that the greatest occurred in the 1.20 gm/cm^3 peak. Tests were performed to substantiate this observation through the use of ^{3}H-uridine-labeling, possible contamination with cell debris or mycoplasm. Results from these studies rule out these possibilities. The procedures employed were examined by the use of ^{3}H-uridine labeled RSV(RAV-1), which demonstrated a radioactive peak at a density range of 1.15 to 1.16 gm/cm^3 in sucrose.

The BV-1 virus produces cytopathic effects in BHK-21 cells when infected cells are incubated with medium containing 10% newborn calf serum. BV-1 virus, (harvested from the chemically infected REL cell line, BV-40), infects REL and BHK-21 cells resulting in the formation of plaques. The plaque assay will allow for cloning and further purification of BV-1 virus.

Studies were completed on viral RNA of the BV-1 and WF-1 viruses. In both viruses, using established extraction procedures, the sedimentation velocity of the RNA was estimated to be 25 to 30S, with approximately 10% of the radioactivity in a region corresponding to 4-10S RNA. RSV(RAV-1) was used as a control in these studies and the expected profiles of 65-70S and 4-10S RNA were obtained. The 25-30S RNA component is suggestive of (a) degradation of the RNA, which is not expected since nuclease inhibitors are used; however, RSV(RAV-1) RNA is not degraded under the same conditions; (b) a subunit structure in the viral genome which is unlike the subunit structure of other C-type viruses; (c) ribosomal RNA of either procaryotic or eucaryotic origin. Experiments are underway to clarify these points.

Significance to Biomedical Research and the Program of the Institute:

Although rats are highly susceptible to spontaneous cancers as well as to the induction of cancers by chemicals and irradiation, and C-type viruses similar to those which cause cancers in other species have been found in rats by electron microscopic studies, no such virus of rat origin has yet been proven to cause a cancer in this species. In addition to the important possibility of having a new laboratory model in another species for guiding approaches to the human virus-cancer problem, the proposed studies would also provide an important test of the Huebner hypothesis that C-type viruses are the determinants of most cancer in all species, including rats and humans for which oncogenic viruses have not yet been demonstrated.

Proposed Course: (1) Further purification studies on BV-1 and WF-1 viruses. (2) Studies on viral RNA. (3) Comparative studies of the biochemical and biological properties of rat C-type viruses (BV-1, R-35, and WF-1) of different origin. (4) Attempts to potentiate the WF cell agent by serial *in vivo* passage of the cells, accompanied by inoculation of rats with cell-free extracts of the tumors.

Date Contract Initiated: June 23, 1967

Current Funding Level: $51,167 (This contract terminates June 30, 1972).

UNIVERSITY OF INDIANA, INDIANAPOLIS, INDIANA (NIH-69-2048)

Title: Characterization of the Twiehaus Agent of Avian Reticuloendotheliosis

Contractor's Project Director: Dr. Alvin S. Levine

Project Officer (NCI): Dr. Michael A. Chirigos

Objectives: (1) To test transmissibility of Twiehaus virus. (2) To determine whether this agent acts as an immunogen. (3) To determine what mitochondrial alterations occur with Twiehaus agent pathogenicity. (4) To determine the presence of reverse transcriptase in this agent.

Major Findings: In day-old cockerels all routes of inoculation (intracranial, intramuscular, intracardiac, intranasal, intraperitoneal, subcutaneous, and via the alimentary canal) were capable of inducing deaths from reticuloendotheliosis virus (REV). From 15 moribund cockerels sampled individually, infectious REV was obtained from oral-nasal washings, gut washings, feather-shaft follicle tips, and skin containing feather follicles, but not from feather dander. Antibody to REV was detected in the serum of contact cagemates. None of the normal control birds, housed separately in the same room, were serologically positive. In spite of the presence of infectious virus in moribund birds and the serologic conversion of the contact mates, horizontal transmission of the disease symptoms was not demonstrated. The results suggest that close contact is required for horizontal transmission of the virus, and that contact with REV in this manner either fails to produce disease or produces a subclinical form.

White Leghorn birds were hyperimmunized with purified, sucrose-banded reticuloendotheliosis virus (REV) of three types: (1) REV from tissue culture (REV-T), (2) sodium dodecylsulfate (SDSO-treated REV-T, and (3) REV purified from liver-spleen homogenates (REV-L). These groups of birds, when challenged with a 10% gravity-settled homogenate of RE-specific liver-spleen homogenate, demonstrated protection against REV at levels of 97%, 77% and 100%, respectively, in the order of hyperimmunizing material listed above. When these same birds were further challenged with cloned strains of Rous sarcoma virus, SR-RSV-B and RSV(RAV-1), REV-T-hyperimmunized birds were protected against these agents at levels of 100% and 93%, respectively. Birds hyperimmunized with SDS-treated REV-T were protected against SR-RSV-B and RSV (RAV-1) at levels of 100% and 29%, respectively. REV-L-hyperimmunized birds were protected against RSV(RAV-1) at a level of 62%. RSV(RAV-1)-immunized birds were not protected against challenge with REV.

In preliminary studies of liver mitochondria from reticuloendotheliosis virus (REV-T) infected chickens, gross alterations were observed in the oxidative and phosphorylative behavior of these organelles. Respiratory activity (Q_{O2}) was greatly diminished and phosphorylative activity, as estimated by state 4-state 3 transitions, in a polarographic apparatus was absent. Succinoxidase activity was enhanced after incubation in an isotonic medium, suggesting large amplitude swelling. Mitochondrial preparations were marked by the appearance of a yellow fluorescent pigment which has not been characterized to date.

It has been postulated that the pathogenicity of REV-T is due to induced emboli. The underlying molecular mechanism may be at the level of the mitochondria, as suggested by these data.

RNA-dependent DNA polymerase activity was originally demonstrated in the virions of avian and murine leukosarcoma virus complexes and has been extended to 27 isolates of oncogenic RNA viruses. Employing published procedure, the Tweihous agent was studied for the presence of the transcriptase. The in vitro DNA polymerase assay used followed the method reported by S. Spiegelman. The results obtained show that the RNA-dependent DNA polymerase is associated with the Tweihaus agent and is similar to that present in the avian leukosarcoma viruses and in other oncogenic RNA viruses.

Significance to Biomedical Research and the Program of the Institute: The avian reticuloendotheliosis virus is a leukemogenic virus prevalent in many flocks of chickens, and is said to be transmitted both horizontally and vertically. The biologic characteristics and the understanding of the chemical, physical and immunological nature of the agent may be applicable to the possible role of viruses as etiologic agents in human neoplasia. Of equal importance is the determination of whether oncogenic viruses of animals have the capabilities to replicate and induce neoplastic diseases in man. The avian viruses must be evaluated for this potential.

Proposed Course: (1) Attenuation of REV(T) for vaccine strain(s). (2) Immunological comparison of REV(T) with other avian tumor viruses. Immunological study of antigen preparations from purified preparations of REV. (3) REV(T) with Marek's disease herpesvirus in vitro and in vivo to determine if interference or potentiation results. These studies are being carried out in collaboration with Life Sciences, Inc. (4) Characterization of REV polymerase(s) and the effect of specific REV(T) antibodies on polymerase activity.

Date Contract Initiated: May 8, 1969

Current Contract Level: $77,485

MELOY LABORATORIES (NIH-72-2020)

Title: Cell Biology Facility: Mechanisms of the Immune Response to Squamous Cell Carcinoma, Adenocarcinoma and Fibrosarcoma in the Mouse; Experimental Immunotherapy.

Contractor's Project Director: Dr. Kenneth Blackman

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To elucidate the mechanisms of the humoral and cellular immune response to different kinds of cancer in the mouse. To develop improved in vitro and in vivo assays for detecting tumor specific antigens and

antibodies. To develop systems of immunotherapy.

Major Findings: Cell-free homogenates of fibrosarcoma induced either SV40 virus or methylcholanthrene will immunize animals against tumor transplant challenge if the cells are first infected with influenza virus. The immunogenic principle in the homogenate is membrane-associated and is still active when formalin-fixed. This influenza virus enhancement of immunogenicity does not occur if egg-grown influenza virus is simply mixed with the tumor homogenate.

A precise radioactive footpad assay for delayed hypersensitivity to tumor cells in the mouse was developed with the use of tumor-immune animals and cell lines produced by the contract. The anti-tumor cell reactivity can be adoptively transferred to normal mice by inoculating them intraperitoneally with spleen cells from tumor-immune mice. Tumor-bearing animals do not show delayed hypersensitivity to tumor after the tumor reaches a certain size.

Twenty-three new transplantable tumor lines of methylcholanthrene-induced fibrosarcoma, twenty of mammary adenocarcinoma, and fifteen of methylcholanthrene-induced squamous cell carcinoma of the skin were developed. All of the tumor lines have been carried through three or more transplant generations. All of the fibrosarcomas and some of the adenocarcinomas possess tumor specific transplantation antigens as determined by tumor-graft rejection assay.

The growth of SV40 induced tumor cells is completely inhibited by admixing spleen cells from tumor-immune animals with the challenge inoculum of tumor cells. Titration experiments show that as few as ten million spleen cells are effective.

Splenectomy has been found to augment resistance to tumor transplant challenge.

Significance to Biomedical Research and the Program of the Institute: The ability to augment the immunogenicity of cell-free tumor homogenates by prior infection of the tumor cells with influenza virus provides a way to isolate immunologically effective tumor transplantation antigens from cell-free homogenates of human tumors so that the patient may be immunized against his own tumor without the drawbacks and risk associated with the inoculation of x-irradiated live cells. Research on the mechanisms of the immunological response to tumor will provide ways of manipulating the immune system to the advantage of the cancer patient both in diagnosis and in therapy.

Proposed Course: The relationship of cell surface structure to tumor-host interaction will be included in future studies.

Date Contract Initiated: August 20, 1971

Current Contract Level: $335,000

MELOY LABORATORIES (NCI-E-72-2006)

Title: Spontaneous and Virus-induced Neoplastic Transformation.

Contractor's Project Director: Dr. John E. Verna

Project Officers (NCI): Dr. George Todaro
Dr. Roy Kinard

Objectives: To study spontaneous and virus-induced neoplastic transformation by the following methods or projects: (1) development and characterization of 3T3 and 3T12 lines from inbred mouse strains; (2) radiation-virus co-carcinogenesis; (3) elucidation of the differences between the normal and transformation prone human cells; (4) characterization of MSV transformed Balb/c 3T3 cells and nonproducer cells; (5) development of assay systems for use in tumor virology; (6) biochemistry of enzymes in tumor viruses; and (7) to search for C-type and B-type RNA viruses in human cells.

Major Findings: The Balb/c and NIH/Swiss embryo cell lines have provided excellent model systems for the study of the effects of tumorigenic viruses both in vitro and in vivo. These cell lines continue to be supplied to numerous investigators throughout the world, and have become the standard cell lines for biochemical and biological investigations of cellular growth control mechanisms.

Human fibroblast cells from patients with a variety of diseases which have been shown to be associated with a high incidence of tumor formation are tested for their susceptibility to transformation by SV40 virus. More than 1200 individual specimens have been cultured for testing. The mechanism which results in the increased susceptibility of certain cells to SV40 transformation appears to be related to a step in SV40 infection which occurs after virus adsorption but prior to the complete uncoating of the virus.

The isolation and characterization of temperature sensitive mutants of viruses associated with the murine leukemia-sarcoma complex is being done in an effort to characterize the gene(s) responsible for transformation and tumorigenicity. Virus assays performed by focus formation of the murine sarcoma virus and by the SC plaque formation test of the murine leukemia virus have been adapted to microtiter procedures. This modification allows the screening of large numbers of potential mutants in a more efficient manner.

Infection and transformation of human cells with SV40 DNA has been established. Different forms of DNA are being tested to define the smallest piece of viral information required for biologic activity.

Cell lines known to release MSV and MuLV continue to be employed as model systems for the study of virus-induced transformation and tumorigenesis. Methods developed in this laboratory led to the successful isolation and identification of a rat-tropic sarcoma virus, M-MSV-O, which possessed a different host range and serologic characteristic than the Moloney sarcoma virus genome.

Human cells derived from normal tissue and malignant tissue of a wide variety of pathological types are being examined by a variety of biochemical techniques. The primary biochemical technique employed is the RNA-dependent DNA polymerase or reverse transcriptase assay. Tests have been developed to distinguish viral enzyme from normal cellular enzymes. Reverse transcriptase assays provide an extremely sensitive measurement of viral expression in normal cells and in cells transformed by murine oncogenic viruses.

It has been possible to detect enzyme activity in normal as well as viral transformed cells. Normal human fibroblasts have been shown to contain polymerase activity. Since normal cells, as well as tumor cells, contain enzymatic activity, further purification was necessary to make the distinction possible. Antibody to known murine viral polymerase has been prepared and shown to be able to inhibit one enzyme from animal tumor cells. Such antibodies do not affect normal cellular enzymes. Thus, it is possible to isolate and identify a viral specific enzyme in virus-producing cells.

Antisera to purified enzymes have also allowed preparation of antisera to a specific viral antigenic component such as the group specific antigens of C-type virus. Such antisera have been prepared and employed for the detection of viral group specific antigens in the ESP-1 human cell line. Expanded research efforts have resulted in the development of methods which greatly increase the sensitivity of detecting viral RNA-dependent DNA polymerase using synthetic templates. The tumor viruses are partially solubilized and polymerase activity which is associated with the internal core of the virus is quantitatively assayed.

Sera from animals possessing tumor induced by murine-virus were found to contain antibody to the polymerase of the murine virus. Antibody against this purified viral enzyme has now been made in rabbits. These antibodies cross-react and inhibit the viral polymerases of several mammalian C-type RNA viruses. The antisera does not cross-react with the enzymes of the avian tumor viruses nor of the mouse mammary tumor virus. It is expected that similar techniques will be useful in identifying a possible human viral enzyme. Extensive screening of viruses for polymerase activity has been performed to determine whether the polymerase is specific for tumor viruses. This has led to the discovery that visna virus and foamy viruses also contain the polymerase activity. Syncytium-forming viruses of several species including the primate, bovine, hamster, and feline have been found to contain an RNA-dependent DNA polymerase.

Significance to Biomedical Research and the Program of the Institute: These studies offer the possibility of determining the sequence of events that occur when a normal cell is converted into a neoplastic cell, suggest a possible simple test for "cancer proneness" in man which would permit recognition of a "high risk" group for cancer in the human population and provide further information at the cellular and molecular level on the "oncogene theory" of cancer.

Proposed Course: Effort on this contract will remain essentially the same.

Date Contract Initiated: May 25, 1965

Current Contract Level: $1,757,000

OFFICE OF PROGRAM RESOURCES AND LOGISTICS

Dr. Jack Gruber, Chief, OPRL, OASDVO, DCCP, Chairman
Dr. David McB. Howell, OPRL, OASDVO, DCCP, Staff Scientist
Dr. Robert J. Goldberg, OPRL, OASDVO, DCCP, Staff Scientist

AUERBACH ASSOCIATES, INC. (NIH 72-2023)

Title: Support Services for Preparation of National Cancer Plan

Contractor's Project Director: Mr. Charles Fricker

Project Officer (NCI): Dr. Jack Gruber

Objectives: To perform a feasibility study of alternate systems for program resources and logistical support management.

Major Findings: This is a new contract. It is anticipated that the contractor will survey participants within the Special Virus Cancer Program to obtain judgments as to the potential applicability and effectiveness of various management approaches to resources and logistics support systems.

Significance to Biomedical Research and the Program of the Institute: To assess the extent to which various types of Resource and Logistics management systems may apply to the management of the National Cancer Program, the National Cancer Institute is interested in surveying those segments of the scientific community which will interface with these systems to obtain value judgments as to the potential applicability and effectiveness of various types of systems. Several approaches are being examined to determine their applicability to the various programs within the National Cancer Program. To provide valid results, a specific NCI Program is being utilized as a model in an applicability survey. In keeping with the above need, this Office is engaged in surveying Viral Oncology Special Virus Cancer Program participants to obtain value judgments as to the potential applicability and effectiveness of several management approaches to a Resources and Logistics support system. It is anticipated that the questionaire developed and the information obtained will be useful in determining effective management options for Resources & Logistics within the NCI Special Virus Cancer Program, and will provide an aid in determining a future NCI course of action relative to similar anticipated programs within the National Cancer Program.

Proposed Course: The contractor is currently preparing an interview guide and questionaire to be utilized in conducting the survey of alternative approaches to resources management.

When clearance has been obtained from OMB, interviews of SVCP participants will be initiated.

Date Contract Initiated: May 18, 1972

Current Annual Level: $25,000

BIOLABS, INC. (NIH 72-2068)

Title: Production of Specified Herpesviruses and the Development of Effective Production and Storage Procedures

Contractor's Project Director: Dr. Clyde R. Goodheart

Project Officers (NCI): Dr. Dharam V. Ablashi
Dr. Robert Holdenried

Objectives: A pilot study will produce, concentrate and purify EBV. The purified EBV will be checked frequently for infectivity after being preserved in various vehicles for long-term storage. Either Herpesvirus Saimiri (HVS) or rabbit lymphoma virus will be used as a model for the above objectives.

Major Findings: The contractor has recently been supplied with Herpesvirus saimiri which he has plaque purified for the production of large quantities of virus to be used in the pilot study. He has also been supplied with two continuous cell lines of owl monkey kidney to be used for HVS production. As the contract has started in the late part of December 1971, it is early to report any major results.

Significance to Biomedical Research and the Program of the Institute: Epstein-Barr virus (EBV) has been found to be a causative agent of infectious mononucleosis, a self-limiting lymphoproliferative disease similar in several respects to acute leukemia or early lymphoma. More importantly, it has been found in very close association with Burkitt's lymphoma, and it appears that all Burkitt cells contain the EBV genome integrated into the host-cell genome. EBV is therefore a prime candidate for the role of a human cancer virus, and this project will devise methods for the optimum production, concentration, and storage of this virus for use in research in the SVCP.

Proposed Course: The HVS will be first produced in large quantity to conduct pilot experiments for concentration and purification purposes. Cells carrying EBV will also be supplied for starting the production of EBV.

Date Contract Initiated: December 20, 1971

Current Annual Level: $79,090

BIONETICS RESEARCH LABORATORIES, INC. (NIH 71-2025)

Title: Investigations of Viral Carcinogenesis in Primates

Contractor's Project Director: Dr. Harvey Rabin

Project Officers (NCI): Dr. Roy Kinard
Dr. Jack Gruber
Dr. Gary Pearson

Objectives: (1) Evaluation of long-term oncogenic effects of human and animal viral inocula in primates of various species, especially newborn macaques; (2) maintenance of monkey breeding colonies and laboratories necessary for inoculation, care and monitoring of monkeys; and (3) biochemical studies of transfer RNA under conditions of neoplastic transformation and studies on the significance of RNA-dependent DNA polymerase in human leukemic tissues.

Major Findings: This contractor continues to produce over 300 excellent newborn monkeys per year. This is made possible by diligent attention to reproductive physiological states of female and male breeders. Semen evaluation, artifical insemination, vaginal cytology and ovulatory drugs are used or tried as needed.

Inoculated and control infants are hand-fed and kept in modified germ-free isolators. They are removed from isolators at about 8 weeks of age and placed in filtered air cages for months or years of observation. The holding area now contains approximately 1200 animals up to 5 years old. Approximately 300 are culled every year at a rate of about 25 per month. This is necessary to make room for young animals inoculated with new or improved virus preparations.

New importance is being given to the New World species of monkeys, including squirrel, marmoset, and spider monkeys. Animals currently on study are being actively culled to reflect this change.

Special emphasis has been placed on virological studies characterizing the Mason-Pfizer monkey virus (M-PMV). Seven sublines established from chronically M-PMV-infected rhesus foreskin cultures were shown to be releasing moderately high titers of infectious M-PMV, and in addition seemed to have undergone in vitro transformation. Inoculation of cells of these sublines into newborn rhesus monkeys produced palpable masses at the sites of inoculation. Biopsies performed on these masses and on the regional lymph nodes of the same animals revealed the presence of proliferating virus characteristic of M-PMV by both electron microscopic and cell culture

analysis. Proliferating M-PMV was found in the lymph nodes of monkeys inoculated with cell-free M-PMV preparations.

Chromatographic examination of transfer RNA's (tRNA's) from control and virus-transformed rat and mouse embryo cells demonstrated differences in phenyl-alanyl-tRNA's and aspartyl-tRNA's. No differences were noted in the elution profiles of seryl-, tyrosyl-, leucyl-, asparaginyl-, or glutaminyl-tRNA.

The effects of 11 rifamycin derivatives on viral reverse transcriptase and on DNA polymerases from human normal and leukemic blood lymphocytes were evaluated. Compound 143-483, 3-formyl rifamycin SV: octyl oxime showed the greatest potency and inhibited all DNA polymerases from both viral and cellular origins.

The contractor also engaged in collaborative studies involving the oncornavirus, RD-114, from a human sarcoma, isolated by Drs. McAllister, Gardiner, and Huebner. The virus is being produced and supplied by Dr. Gilden of Flow Laboratories. Another virus, a human papovavirus associated with progressive multifocal leukoencephalopathy, is being supplied by Dr. Duard Walker for inoculation into newborn monkeys.

Significance to Biomedical Research and to the Program of the Institute: Inasmuch as tests for the biological activity of candidate human viruses will not be tested in the human species, it is imperative that another system be developed for these determinations and subsequently for the evaluation of vaccines or other measures of control. The close phylogenetic relationship of the lower primates to man justifies utilization of these animals for these purposes. Further study of altered transfer RNA and polymerase enzymes would determine their significance in neoplastic change and provide a basis for selection of therapeutic agents.

Proposed Course: The previously mentioned studies will be continued and expanded. Particular attention will be given to research on animals inoculated with candidate human cancer viruses, and investigations will be carried forward into the nature of neoplastic changes and their possible control at the cellular level. Collaborative efforts with other researchers within the SVCP will continue.

Date Contract Initiated: February 12, 1962

Current Annual Level: $2,153,850

CALIFORNIA, UNIVERSITY OF (PH43-63-13 and NCI-FS-8)

Title: Development and Evaluation of Cell Substrates for the Study of Cancer Viruses

Contractor's Project Directors: Dr. Stewart Madin
Dr. Neylan Vedros
Dr. Adeline Hackett
Dr. Walter Nelson-Rees
Dr. Helene Smith

Project Officer (NCI): Dr. James T. Duff

Objectives: The Cell Culture Laboratory (CCL) is physically located at the Naval Biomedical Research Laboratory (NBRL), in Oakland. The program of the CCL is funded by a contract (43-63-13) between the University of California and the NCI. In addition, maintenance and operating expenses generated by the CCL are repaid to NBRL by an interagency transfer of funds (FS-8) between NCI and NBRL. The research studies include the development and evaluation of cell substrates for the study of cancer viruses, development of large quantities of specific cell substrates, karotyping of cell cultures, and performing biophysical, virological, and cytogenetic research.

Major Findings: The contractor has distributed 1,072 ampoules or flasks of cell cultures to 117 recipients, primarily within the Special Virus Cancer Program, this year. The contractor's latest catalogue lists 1,254 cell substrates initiated or propagated and stored in this laboratory for distribution following antibiotic-free cultivation, characterization and assurance of species specificity, and freedom from microbial contamination.

The electron microscopic survey of cell lines for virus particles has been largely negative. However, EB virus particles were found in one cell line derived from tumor cells from a case of Hodgkin's disease. In addition, two other human cell lines derived from paracentesis fluid of a breast carcinoma and a breast adenocarcinoma showed signs of producing virus when examined by electron microscopy and DIPIC (demonstration of isotope labeled particles by isopycnic centrifugation). These developments will be pursued further.

The contractor has developed techniques for selection and cultivation of epithelial-like cells in vitro which apparently exclude fibroblastic cells.

Dimethyl-benzyl-rifampicin has been found to be extremely effective in reducing the transformation of mouse cells by MSV without affecting cell growth. In addition, this antibiotic inhibits the transformation of cells resulting from rescue of

a sarcoma genome, while leukemia virus production is not affected. These results support the idea that viral transformation of cells is independent of infectious virus production and that cellular enzyme systems other than the RNA-directed DNA polymerase of the virus are involved.

The contractor has developed a simplified assay system for leukemia virus, the NP-UCI cell line, which serves as an indicator of MLV replication and is as sensitive as the B/3T3+XC cell assay.

Clones of BALB/3T3 cells which were abortively transformed by SV40 have been grown to mass culture. These cells display normal growth characteristics, lack SV40 T antigen, and do not release SV40 upon fusion with monkey cells. However, despite the lack of any obvious manifestation of the viral genome, tests of these cells by DNA-DNA hybridization have revealed that two of the lines each contain several apparently complete copies of the SV40 genome per cell. Experiments with these "cryptic transformants" are continuing.

Chromosome monitoring of cell cultures continues for in-house production and experimentation, and in collaborative efforts, as well as for karyotype reference.

Proposed Course: Continue to develop cell reagents as substrates for human carcinogenesis; attempt to isolate and characterize viral agents from human tumor cells; continue a reference laboratory karyology of cells in culture; study oncogenic viral antigens during embryogenesis and continue basic research in the biology of tumor viruses.

Significance to Biomedical Research and the Program of the Institute: The contractor has developed an excellent tissue culture facility and is supplying cell cultures for cancer research studies to NCI investigators and SVCP contract laboratories. These studies are oriented toward a study of the fundamental biology of tumor cells, and the interaction between tumor cells and viruses of oncogenic importance.

Date Contract Initiated: October 1, 1962

Current Annual Level: $438,000

UNIVERSITY OF CALIFORNIA AT SAN DIEGO (NIH 70-2202)

Title: Development and Operation of a Breeding Colony of Domestic Cats

Contractor's Project Director: Dr. Alexis J. Kniazeff

Project Officers (NCI): Dr. Robert Holdenried
Miss Marie Purdy

Objectives: To develop and operate a permanent breeding colony of cats which will supply offspring for cancer research.

Major Findings: The operation of the colony has been, in general, more successful this year than last. The improvement can be ascribed to better sanitation, better disease control, and a lower abortion rate among hormone-treated cats. As a result, the colony produced 136 pregnant animals, of which 114 were supplied to various SVCP investigators, the remainder being used for studies in the contractor's laboratory.

The induction of oestrus in cats at the facility is still being carried out by means of equine gonadotrophin. Limited studies have been initiated in this laboratory to adjust empirically the level of the drug to the hormonal state of the animal during different periods of the season. In addition, experiments are in progress to attempt to establish a single dose of gonadotrophin which would produce a satisfactory induction of estrus during the off-season months.

Arrangements are now being made to initiate the screening of cats, which will eventually be shipped in pregnancy to SVCP investigators, for their viral antibody spectrum. It is hoped that such information will facilitate the work of various investigators who use these animals, particularly those involved with vaccine studies.

Significance to Biomedical Research and the Program of the Institute: This colony provides a major source of pregnant cats used in the Special Virus Cancer Program for feline leukemia-sarcoma studies. The cat remains an important animal for cancer research, as demonstrated by the fact that a candidate human cancer virus, RD-114, was first demonstrated in tumors from kittens which had been inoculated before birth with human cancer tissue.

Proposed Course: The contractor proposes to continue operations to provide pregnant cats to laboratories within the SVCP along the previously described lines.

Date Contract Initiated: June 25, 1969

Current Annual Level: $172,700

CHICAGO PARK DISTRICT, LINCOLN PARK ZOO (PH43-65-1017)

Title: Marmoset Breeding Colony

Contractor's Project Director: Dr. Lester E. Fisher

Project Officers (NCI): Dr. Jack Gruber
Dr. Roy Kinard

Objectives: To provide marmosets in a quantity and quality sufficient for the needs of the research on tumor viruses conducted under Contract NIH-71-2032 with Rush-Presbyterian-St. Luke's Hospital.

Major Findings: There are now 53 breeding pairs in the colony. Production continues at the rate of at least 120 births per year with no problems.

Significance to Biomedical Research and the Program of the Institute: This contract is part of a program utilizing lower primates for testing selected laboratory specimens for oncogenic activity. The marmoset, a small, inexpensive primate, has been shown to be susceptible to several cancer viruses; newborn and young animals are in demand by SVCP investigators.

Proposed Course: The project will be continued to insure the availability of experimental animals of quality.

Date Contract Initiated: June 28, 1965

Current Annual Level: $24,059

UNIVERSITY OF COLORADO MEDICAL CENTER (NIH 69-2080)

Title: Collection of Pediatric Tumor Specimens

Contractor's Project Director: Dr. William E. Hathaway

Project Officer (NCI): Dr. Paul H. Levine

Objectives: To obtain tissues and serum specimens from pediatric oncology patients and suitable controls for collaborative studies with the SVCP.

Major Findings: Tissue, sera, and appropriate clinical information were sent to investigators within the SVCP from the contractor's pediatric sources. Specimens were made available from a wide variety of patients with diagnoses including leukemia, lymphoma, rhabdomyosarcoma, osteogenic sarcoma, hepatoma, neuroblastoma, and a variety of brain tumors. Two identical twins with acute leukemia and their families were evaluated for evidence of leukemia-associated antigens and skin fibroblast transformations. A unique family with a marked history of Fanconi's anemia was completely studied by chromosome analysis and skin fibroblasts were sent

for susceptibility to SV-40 transformation. In addition, specimens were available from families with multiple cases of cancer, a nursing mother with a history of Hodgkin's disease, a patient with several documented episodes of infectious mononucleosis prior to Hodgkin's disease and tissues from a patient with Jacob-Kreutzfeldt disease (a neurological degenerative disease caused by a slow virus) were provided to SVCP.

Collaborative studies have been undertaken to utilize the organization of a program on Hodgkin's disease and osteosarcoma throughout the city of Denver. Specimen collection is in progress for lymphocyte-mediated immunity studies, HLA typing, and serology. Historical data are being collected to evaluate the possible role of genetics, environmental factors, and manipulation of the immune system (particularly through tonsillectomy and appendectomy) in the etiology of Hodgkin's disease.

Significance to Biomedical Research and the Program of the Institute: This is a pediatric research contract of major importance to the SVCP, since it is a primary source of pediatric cancer specimens for NCI and other SVCP researchers on the East Coast. A continuing supply of such specimens is absolutely necessary to the pursuit of the viral etiology of human cancer.

Proposed Course: Continue to collect serum and tumor specimens as in the past. Immunological investigations, using fresh lymphocytes and tissues, will be continued by the contractor. Additional personnel are being made available to collect specimens from adults with cancer, as well as children. In addition, individuals with high risk to neoplasms will be investigated for host factors which increase the possibility of developing cancer. Materials will be sent to NIH for virological and immunological studies.

Date Contract Initiated: June 18, 1969

Current Annual Level: $115,299

UNIVERSITY OF CONNECTICUT (NIH 69-52)

Title: Development and Maintenance of a Specific Pathogen Free Flock of White Leghorn Chickens

Contractor's Project Director: Dr. Roy E. Luginbuhl

Project Officers (NCI): Dr. Robert Holdenried
Dr. Roy Kinard

Objectives: Establish and maintain a flock of chickens free of specified pathogens, including avian leukosis viruses, and to provide eggs for research use.

Major Findings: Approximately 13,000 eggs and cell cultures in addition were provided to cancer research. A few of the recipients were Drs. J. Beard, M. Green, H. Morgan, F. Deinhardt, P. Sarma, and G. S. Beaudreau. Fifteen specially characterized breeding birds were supplied to Dr. Beard's group.

There is no serologic evidence of the following organisms or diseases in the SPF flocks: Mycoplasma gallisepticum and synoviae, Salmonella pullorum, Newcastle disease, avian infectious bronchitis (Connecticut and Massachusetts strains), infectious laryngotracheitis, avian encephalomyelitis, CELO virus, and the three serotypes of RSV. There have been several birds displaying lesions characteristic of Marek's disease (MD), and MD viral antibodies have been detected in some flocks using the agar gel precipitin test. Nevertheless, one new flock consisting of 26 birds remains free of antibodies at four months of age. Several flocks have been characterized as gs antigen negative or as gs antigen positive. The gs status of these flocks' offspring can be reliably predicted, indicating a simple recessive genetic control for gs expression.

Significance to Biomedical Research and the Program of the Institute: The methods being developed indicate that eggs free of specified infectious organisms can be produced. A significant portion of the avian leukosis research in the United States is dependent on the continued availability of this highly controlled and monitored flock.

Proposed Course: Continued maintenance of the flock, with development of genetic lines of chickens characterized for the susceptibility of their embryos to leukosis virus. Reestablish flocks free of MD virus and continue work to provide genetically gs characterized birds.

Date Contract Initiated: June 18, 1962

Current Annual Level: $92,400

NEW YORK STATE VETERINARY COLLEGE AT CORNELL UNIVERSITY (NIH 70-2224)

Title: Feline Tumor Viral Diagnostic Laboratory

Contractor's Project Director: Dr. James H. Gillespie

Project Officer (NCI): Dr. James T. Duff

Objectives: To produce and evaluate cat viral reagents; to monitor cat cell cultures and other materials associated with cat tumors for indigenous cat viruses and other microorganisms.

Major Progress: During the previous year the contractor's packaged feline viral reagents have been titrated in a feline kidney cell line and the serum neutralizing titers of the packaged goat antisera to these viruses have been determined in the same kidney cell line (see October and June 1971 reports). The serologic relationships between the 14 strains of feline picornaviruses are still unclear. As previously reported there is a great degree of cross reactivity between these 14 strains and present effort is directed toward further testing to clarify these relationships.

The contractor has made available to the American Type Culture Collection bulk samples of a number of the feline viral reagents (Feline picornavirus strains FJ, 68 FIV [CFI], FRI-14, KCD, 5 FPL [Bolin] and 17 FRV) as well as the Carmichael strain of canine herpesvirus. Test samples of these agents were lyophilized by the ATCC and returned for titration. Results indicate that these viruses withstood lyophilization reasonably well and that this method of preservation might be considered for storage of these agents.

Stocks of feline herpesvirus were produced for a participating laboratory to enable them to evaluate a serologic response in leukemia infected cats. Study of the hemagglutinating properties of the feline herpesvirus (C_{27} 10 FVR) is continuing with the expectation of developing a standard hemagglutination inhibition test for the assay of antibody to this agent.

The feline tumor material monitoring phase of the contract program has been quite active during the past reporting period. The contractor has undertaken to do the monitoring for indigenous feline viruses for the NCI-participating laboratory of Dr. Vivian Larsen at Merck Sharp & Dohme. To date over 400 samples have been processed; moreover, additional samples of tumor cell cultures and related materials from a number of participating laboratories have been and are in the process of being screened for the presence of indigenous feline viruses.

Significance to Biomedical Research and the Program of the Institute: This laboratory is a major source of reagents and expertise concerning the feline tumor viruses, and makes both available to scientists within the SVCP. The contract provides a central laboratory where materials isolated from normal cats

and cats suffering from cancer can be sent to determine if they contain indigenous feline agents, as well as for viral identification.

Proposed Course: Additional characterization of feline virus reagents will be carried out; work will also be continued on the hemagglutination and hemagglutination-inhibition tests for feline herpesvirus. The laboratory will continue to monitor any material sent by SVCP researchers for the presence of indigenous or contaminant feline viruses, and will prepare stocks of feline viruses for SVCP laboratories upon request.

Date Contract Initiated: June 25, 1970

Current Annual Level: $42,000

DUKE UNIVERSITY (NIH 71-2132) DURHAM, NORTH CAROLINA

Title: Study and Production of Avian Leukosis Virus

Contractor's Project Director: Dr. Joseph W. Beard

Project Officer (NCI): Dr. Michael A. Chirigos

Objectives: The objectives of this project are: (1) to continue quantity and quality production of BAI strain A avian tumor virus; (2) to continue investigations on RNA avian leukosis viruses. The contractor projects a monthly production of 35 gms wet weight of plasma and 55 gms wet weight of tissue culture grown BAI strain A avian tumor virus. They will investigate in in vivo (chickens) and cell culture systems other avian viruses which include: sarcoma (without hematopoietic disease); erythroblastosis (and associated growths); myeloblastosis (and associated growths) and myelocytomatosis (and associated growths). Avian leukosis virus strains BAIA, R, ES4, and MC-29 will be employed in these studies. The contractor will employ a multidisciplinary approach to the studies of avian tumor viruses including: biochemistry, tissue culture, virology, electron microscopy, pathology, and immunology.

Major Findings: The major work has been the production and distribution of BAI Strain A (myeloblastosis) virus and leukemia myeloblast cells. A total of 244,929 mg. wet weight of plasma virus and 439,826 mg. wet weight of tissue culture virus has been distributed to 53 investigators. Those receiving more than 15 grams of virus are: S. Spiegelman, 78,572 mg. pv, 252,654 mg. tcv; M. Green, 1,646 mg. pv, 83,301 mg. tcv; J. Hurwitz, 17,221 mg. pv, 19,088 mg. tcv; R. Gallo, 21,380 mg. pv, 1,368 mg. tcv; P. Zamecnik, 20,547 mg. pv, 1,522 mg. tcv; D. Bolognesi, 16,774 mg. pv; K. Stromberg,

15,698 mg. pv; G. Todaro, 15,240 mg. pv.

In addition to producing large quantities of virus, the contractor has contributed to the preparation of specific products of AMV, e.g., purified gs antigen, labeled RNA, intact un-nicked RNA for end-group analysis, 62S viral RNA, etc., in response to requests from SVCP researchers.

The contractor has continued research on leukosis virus. Histologically the MC-29 strain has proven to be a most unusual leukosis agent with an especially broad spectrum of tumors not induced by any other avian tumor virus. Aside from the myeloid malignancy induced by MC-29, hepatocyte transformation and renal growths have also been observed. Of particular significance to the polymerase studies being conducted with AMV, it is interesting to note that AMV activity to induce myeloblastosis can be transmitted by virus particle-free RNA preparations. In vitro and in vivo investigations have shown that the MC-29 strain or a component of this strain passes properties of defectiveness similar to those of Bryan high titer Rous sarcoma virus.

A major portion of the contract consists of a detailed analysis of RNA tumor virus particles and their interactions with the host cell. Viral polypeptides are being purified for analysis of their amino-acid sequence and for preparation of specific antisera for analyzing virus antigens in infected cells. Preparations of AMV virus particle cores have been shown to be infectious for chick embryo cells in culture. Since AMV, however, is a non-focus forming virus, attention is being directed toward development of techniques to isolate cores from focus-forming viruses, and positive results have been obtained with the MC-29 virus.

Significance to Biomedical Research and the Program of the Institute: One of the major objectives of the SVCP is to explore fully all important animal model systems for the determination of the possible viral etiology of cancer in man. Avian tumor viruses induce a variety of diseases similar to those which occur in man (erythroblastosis, myeloblastosis, myelocytomatosis, reticuloendotheliosis, and sarcomas); the causative viruses have been isolated and the disease can be induced in vivo under controlled conditions which permit the study of the immunology, virology, biochemistry and therapy of the tumor virus complex. Moreover, BAI Strain A avian tumor virus is the only RNA C-type virus which is at present available in large enough quantities to permit exhaustive investigation into the biochemical makeup and behavior of both the virus and its components. As such, it represents an important model for the C-type viruses of higher animals and is an essential tool in the search for cancer viruses in man.

Future studies will depend upon large quantities of concentrated virus, which the contractor is uniquely in a position to supply.

Proposed Course: The contractor will continue to meet requests for virus and viral components, and will extend and expand the research outlined above.

Date Contract Initiated: April 19, 1971

Current Annual Level: $650,000

ELECTRO-NUCLEONICS LABORATORIES (NIH 71-2253)

Title: Development of Propagation Procedures, Purification and Characterization of Viruses

Contractor's Project Director: Mr. John Lemp

Project Officer (NCI): Dr. George Todaro

Objectives: To develop propagation procedures to produce high virus yields from cell cultures, and to purify, determine particle count per ml, and otherwise characterize the produced virus.

Major Findings: This contract was initiated on May 28, 1971, to provide the SVCP with a facility close to NCI where relatively large volumes of fluid containing RNA tumor viruses could be harvested from cell cultures, purified, and concentrated, and the cultures and their products studied and evaluated by electron microscopy.

The contractor has thus far cultured 38 cell lines. He has processed 1,570 liters of tissue culture fluid, from which he has obtained 423 ml. of highly concentrated tumor viruses of various kinds. These virus concentrates have been sent to researchers within the SVCP.

Significance to Biomedical Research and the Program of the Institute: The search for evidence of the viral etiology of human cancer must include studies on viruses present in cell cultures established from animal tumors as well as on those candidate human cancer viruses growing in either animal or human cell cultures. Large volumes of these well-characterized and concentrated viruses are essential for the preparation of specific antisera and for the biochemical, immunological, and epidemiological investigations necessary in cancer virus research.

Proposed Course: To continue the propagation of cell lines and the harvest of virus as directed by the Project Officer.

Date Contract Initiated: May 28, 1971

Current Annual Level: $403,000

ELECTRO-NUCLEONICS INC. (NIH 72-3249)

Title: Large-Scale Production of Oncogenic Viruses

Contractor's Project Director: Mr. John Lemp

Project Officer (NCI): Dr. Jack Gruber

Objectives: To provide research and services related to the isolation, large-scale production, concentration, and assay of oncogenic viruses of animals and potentially oncogenic viruses of humans; production and quality control will involve tissue culture, electron microscopy, immunology, and various biochemical/biophysical techniques.

Major Findings: Since this is a new contract, activated in the latter part of FY '72, there are no major findings to report.

Significance to Biomedical Research and the Program of the Institute: In order to carry out important research on the biochemistry and biophysics of oncogenic animal viruses, it is imperative that large quantities of concentrated virus be available for analysis. This contract will help meet this need with oncogenic animal viruses that have been produced under rigidly controlled conditions, and will also serve to find the best means of producing and concentrating large quantities of new candidate human cancer viruses as they are discovered.

Proposed Course: Initial production will be of Rauscher leukemia virus at a volume of 50 liters/week; eventually, production will reach a volume of 150 liters/week. Additional viruses will be produced as program needs dictate.

Date Contract Initiated:

Current Annual Level: $145,000

EMORY UNIVERSITY, YERKES PRIMATE CENTER (NIH 71-2256)

Title: Maintenance of a Colony of Irradiated, Aging Rhesus Monkeys

Contractor's Project Director: Dr. Harold McClure

Project Officer (NCI): Dr. Roy Kinard

Objectives: To determine the incidence of tumors in a unique group of irradiated, aging rhesus monkeys and to supply tissue from tumors for transplantation, tissue culture and virus isolation to SVCP collaborators.

Major Findings: A group of 72 rhesus monkeys with adults ranging in age from 12 to 18 years remain from an earlier study on the effects of irradiation. Forty-seven animals received irradiation in 1956-1958, and 16 are non-irradiated controls. The remainder are non-irradiated offspring born in the last four years.

Two animals have developed malignant tumors, an adenocarcinoma and a seminoma, respectively. Samples of these tumors have been sent to Dr. Thomas Kawakami of the University of California and to Dr. John Landon of Bionetics, Inc. Serum samples have been collected from all 72 animals in the study and shipped to Dr. Kawakami for screening of both viral antigens and antiviral antibodies.

Significance to Biomedical Research and the Program of the Institute: The SVCP conducts collaborative projects for the study of relationships between the etiologies of tumors of various primates. This project provides tumor tissues and other important specimens from aging non-human primates which have been subjected to irradiation to researchers within the SVCP. At the same time the contractor conducts a screening operation for the appearance of virus-like particles or viral antigens in the monkeys. Malignant changes in these primates may provide useful information which might be applied to humans, who are also subjected to various forms of radiation as well as to the natural aging process.

Proposed Course: The entire group of monkeys will continue to be monitored for neoplasia by physical and hematologic examinations. All tumors which develop will be evaluated by the contractor by light and electron microscopy. Specimens from these tumors will also be made available to other SVCP investigators. In addition, a breeding program is being initiated to evaluate the incidence of leukemia or other tumors in infants with aging and irradiated parents.

Date Contract Initiated: May 1, 1971

Current Annual Level: $24,000

FLOW LABORATORIES, INC. (PH43-65-1012)

Title: Maintenance of a Repository for Storage and Distribution of Reagents and Tissue Specimens

Contractor's Project Director: Mr. Jack W. Walker

Project Officer (NCI): Miss Marie E. Purdy

Objectives: To provide for the SVCP a centrally located low temperature storage and distribution center for viral reagents and tissues.

Major Findings: In 1971, the contractor made 318 shipments of viral reagents and tissues which comprised a total of 10,220 vials of material. He received 51 shipments of similar materials which comprised 25,366 vials. All incoming shipments were carefully checked for damage in transit and were catalogued before being placed in the low temperature repository.

No problems which might interfere with the efficient operation of the contractor's activities have been reported.

Significance to Biomedical Research and the Program of the Institute: An efficient research program must have readily accessible adequately characterized resource materials. The storage and shipping facilities operated under this contract enable the scientist to have access to a large inventory of special research materials without the burden of procurement, storage, inventory, and distribution.

Proposed Course: It is anticipated that the repository activities will continue to grow in the future as the Program increases in scope.

Date Contract Initiated: June 22, 1965

Current Annual Level: $115,420

FLOW LABORATORIES, INC. (NIH 71-2341) ROCKVILLE, MARYLAND

Title: Animal Holding Facility to Support Intramural Research on RNA Viruses and Autoimmune Diseases

Contractor's Project Director: Dr. William A. Knapp

Project Officer (NCI): Dr. Adi Gazdar
Dr. John W. Pearson

Objectives: The objective of this contract is to support ongoing activities in the Virus and Disease Modification Section, VBB, NCI and the Viral Pathology Section, VLLB, NCI. The nature of the above activities require supportive services which this contract provides. In general, the contractor will receive and maintain mice, rats, hamsters and other small animal species as required for the purpose of observation and experimentation during the aging process for the following research studies: (a) Development of autoimmune disease, (b) Relationship of autoimmune disease to oncogenic viruses, (c) Development of spontaneous cancers and their modification to chemo-immunotherapeutic agents, and (d) Immunologic responsiveness to immuno-enhancers and/or suppressors.

Major Findings: Since the initiation of this contract on June 15, 1971, the contractor has received 5866 mice, 1801 rats, and 4 rabbits which are being used in two projects. The first project comprises immunostimulation studies on AKR mice, to which single and multiple injections of BCG and Corynebacterium granulosum are administered over a period of time in order to prolong the time to onset of spontaneous lymphocytic leukemia. This research is at too early a stage to permit definite conclusions. In addition, the project includes the use of combination drug therapy against spontaneous leukemia in AKR mice in order to induce remission. Having succeeded in obtaining remission, the investigators are now treating the animals with single or multiple injections of BCG or Corynebacterium granulosum in order to extend the period of remission and/or obtain long term survivors of the disease.

The first project also includes studies in which rats are inoculated with various malignant cell lines, treated with drugs after a tumor appears, and then given BCG or C. granulosum if remission occurs. The cell lines include Dunning tumor cells, Nova leukemia cells, Gross leukemia cells, and Moloney sarcoma cells. These studies are still at an early stage.

Investigations are also being carried out which involve immunological studies on the C-type viruses associated with different rat tumor cell lines (R-35, WF-1, and RMTL-8). The results of immunofluorescence experiments, verified by absorption studies, indicate that the rat viruses associated with these different cell lines are antigenically identical or closely related.

The second project in this contract involves a study of oncogenic viruses and interferon inducers on autoimmune disease in NZB/WF_1 mice. This study is still at an early stage.

Significance to Biomedical Research and the Program of the Institute: The major goals of SVCP program are: (1) to detect and isolate tumor viruses, (2) the prevention and control of virus-induced malignancies in man as well as in animals associated with him. Current in-house efforts are underway to investigate the relationship of the aging process and autoimmune disease states to spontaneous and virus-induced malignancies. In addition, ongoing investigation utilizing chemo-immunotherapeutic approaches are being studied in both rat and mouse leukemia and tumor model systems. It is expected that the information resulting from this research will have considerable application in studies on similar diseases in man.

Proposed Course: It is intended to engage in inoculation, palpation, blood smears, sera collection, eye bleedings, autopsies, and harvesting and processing of tumors in mice, rats, and hamsters, and to continue maintenance of these animal colonies for long-term studies on (1) autoimmune disease in New Zealand mice, (2) development of spontaneous cancer in AKR mice and their modification by chemo-immunotherapeutic agents, and (3) immunological responsiveness to immunoenhancers, i.e. BCG, Corynebacterium granulosum, interferon stimulators, and/or immune cell transfer alone or in combination with drug therapy in various mouse and rat leukemia tumor systems.

Date Contract Initiated: June 15, 1971

Current Annual Level: $85,485

GEORGETOWN UNIVERSITY (NIH 72-3248)

Title: Supply of Blood and Tissue Specimens from Patients with Malignancies

Contractor's Project Director: Dr. Gerald Sandler

Project Officer (NCI): Dr. Paul Levine

Objectives: To collect fresh blood and tissue specimens from patients suffering from various neoplasias.

Major Findings: Since this new contract was activated in the latter part of FY '72, there are no major findings to report.

Significance to Biomedical Research and the Program of the Institute: It is vitally important that a continuing supply of specimens from patients suffering from neoplasias be available to researchers seeking the viral etiology of cancer. This contract is particularly advantageous because the contractor is located within a few miles of NCI. This

proximity will allow the formulation and alteration as necessary of particularly detailed protocols, and will also allow for the availability of very fresh specimens to SVCP researchers in the Washington area.

Proposed Course: Procurement as described.

Date Contract Initiated:

Current Annual Level: $16,517

GERMFREE LIFE RESEARCH CENTER (PH43-65-95) FT. LAUDERDALE, FLORIDA

Title: Germfree Research and Operation of a Collaborative Germfree Tumor Virus Laboratory

Contractor's Project Director: Dr. Joel Warren

Project Officer (NCI): Dr. M. A. Chirigos

Objectives: The activities under this contract are of three different types, each involving the special germfree and environmentally controlled SPF facilities and capabilities of the contractor: (1) Service type activities in general support of SVCP and intramural research requiring clean, defined animals and viral reagents; (2) Participation in collaborative research primarily of other groups, but in which germfree and/or rigid SPF environmental control are required for definitive results; and (3) Research primarily by contractor scientists, but of mutual interest to the SVCP or collaborative with other SVCP groups where back-up in other special disciplines are necessary. Specific objectives under (1) are: (a) Production of tumors in germfree avian and rodent animals by chemical carcinogens and propagation of such tumors by transplantation as a resource for studies of such tumors by other investigators. (b) Production of oncogenic viruses in germfree animals as a source of "reagent grade" virus for use in SVCP research, including that in this contractor's facility. (c) Supply of limited number of germfree animals to other investigators where feasible, as a spin-off from maintenance of the foundation colonies.

Major Findings: During the past year, numerous germfree (GF) and specific pathogen-free (SPF) animals have been sent to various researchers. Among these are: Dr. Robert Huebner, SPF Graffi hamsters; Dr. Sol Spiegelman, GF Fischer rats; Dr. William Moloney, SPF Fischer rats: Dr. Padman Sarma, GF Fischer rats; Dr. John Pearson, Fischer rats; Dr. Vernon Riley, GF BALB/c mice and GF Fischer rats; Dr. V. Saurino,

GF BALB/c mice and SPF Japanese quail; and others. Reagent grade colonies of germfree and SPF Fischer and Sprague-Dawley rats, BALB/c mice, Graffi hamsters, and Japanese quail continue to be maintained, monitored, and distributed at the request of intersted laboratories. The germfree colonies continue to be free from virus particles as determined by electron microscopy.

The contractor has found that inoculation of tobacco tar condensate into the pectoral muscle of germfree quail failed to induce neoplasia after 18 months. However, a single intramuscular injection of certain tars will accelerate and intensify the response to a subsequent inoculation of Rous sarcoma virus (RSV). The ability of tobacco tar condensate to potentiate RSV infection in quail might provide a rapid and reliable assay of potential carcinogenic activity. Tests of 20 coded samples of different tars indicate that certain preparations are more active than others in repeated assays.

Dimethylsulfoxide (DMSO) has been found to potentiate MSV infection in mice if it is incorporated into drinking water at 2% concentration. However, the same concentration of DMSO in the drinking water of rats delayed the development of transplantable leukemia in Fischer rats and markedly suppressed it in Sprague-Dawley rats.

Prolonged exposure of rat embryo fibroblast cultures to an "active" tobacco tar and subsequent inoculation of the cultures into weanling Fischer rats has given rise to tumors in three of five animals four months later. Similar cultures exposed to an "inactive" tar have not produced any symptoms to date.

Significance to Biomedical Research and the Program of the Institute: The study of many of the most important problems in the virus causation of cancer in animals requires the use of certified animal hosts free of extraneous viruses and other pathogenic microorganisms, as well as skilled technical operations within evnironmentally controlled facilities, including completely germfree isolators for some purposes.

This contract supports critical studies in such animals of interactions among viruses in dual infections (e.g., interference, enhancement, "helper" action), and cocarcinogenic activity between viruses and chemical compounds, both of which underlie the development of knowledge and technology for the detection and isolation of oncogenic viruses of man.

Future Course: To continue to develop, maintain, and distribute colonies of germfree and SPF mice, rats, and hamsters as required by SVCP projects. To continue to serve as the

nucleus colony for other contracts and intramural laboratories. To continue the production of "reagent grade" lots of the Vogt strain of RSV in germfree quail for use in research in this and other SVCP contracts; appropriate bacteriological and histopathological monitoring will be continued.

Date Contract Initiated: April 16, 1965

Current Annual Level: $110,910

HEALTH RESEARCH INC. (RPMI) (NIH 72-3247)

Title: Procurement of Leucocytes and Tissue Specimens for the SVCP

Contractor's Project Director: Dr. Joseph Sokal

Project Officer (NCI): Dr. Paul Levine

Objectives: To collect tissues and blood samples from adults suffering from neoplastic hematologic disorders, particularly Hodgkin's disease and leukemia, for use by researchers within the SVCP.

Major Findings: Since this new contract was activated in the latter part of FY '72, there are no major findings to report.

Significance to Biomedical Research and the Program of the Institute: A major goal of the SVCP is to identify, isolate, propagate, and characterize candidate human cancer viruses. Of paramount importance in the efforts to reach this goal is the continued availability of clinical specimens and histories from patients suffering from cancer. This contractor, who sees a large number of these patients annually, is in an excellent position to help meet increasing program needs for large quantities of human neoplastic specimens.

Proposed Course: Procurement as described.

Date Contract Initiated:

Current Annual Level: $15,000

HOSPITAL FOR SICK CHILDREN (PH43-65-97)

Title: Human Leukemic and Normal Tissue Collection and Preservation

Contractor's Project Director: Dr. Peter McClure

Project Officers (NCI): Dr. Paul H. Levine
Dr. Charles W. Boone

Objectives: To obtain serum and plasma specimens for a wide variety of research purposes from pediatric leukemics, relatives of such patients, and non-leukemic controls.

Major Findings: In accordance with the serum collection program, 491 samples were collected from 34 untreated acute leukemia patients, 32 "normal" controls, 31 hematological controls, 269 first degree relatives of leukemic patients, and 125 previously diagnosed leukemic patients. 548 special samples were collected from long term survivors with acute leukemia, pediatric patients with solid tumors and their first degree relatives, and a special group of normal controls. In addition to the increased number of serum samples processed, a collaborative study on leukemia in twins was continued with NCI investigators.

Significance to Biomedical Research and the Program of the Institute: As the largest pediatric hospital in North America, this contractor supplies many vital serum specimens to SVCP not readily available elsewhere. The contractor also provides an important service to Program by collecting numerous samples of tissue for uses in which the unavoidable delay in passage through customs is not critical. In addition, the contractor consistently refers patients to NCI for study whose cases are felt to be particularly relevant to the research needs of program.

Proposed Course: The contractor will continue to seek other patients of interest, and will continue to collect serial specimens from pediatric patients and family members. Virological and immunological studies on the twin families already identified will also be carried forward.

Date Contract Initiated: February 3, 1965

Current Annual Level: $15,000

HUNTINGDON RESEARCH CENTER (NIH 69-54)

Title: Development of Oncogenic Virus Diagnostic Reagents and Services

Contractor's Project Director: Dr. Roger E. Wilsnack

Project Officer (NCI): Dr. Robert Holdenried

Objectives: To develop, produce, and characterize special diagnostic reagents for use in the SVCP, primarily antisera and antisera conjugates to viruses, GS antigens, globulins of various animal species, and to T-antigens of polyoma and SV40 in tumored hamsters.

Major Findings: This year, as well as last, tumored Fischer rat MSV(M) antiserum was the most heavily and widely used of the reagents produced by the contractor. However, the contractor also continued to produce and characterize antisera against a very wide array of antigens encountered in cancer research, and added a number of antisera to his inventory during the year. These included new antisera against human immunoglobulins, porcine gamma globulins, murine leukemia virus, and feline leukemia virus. He also provided a sensitive means for the identification of group-specific (gs) antigenic activity by comparison of precipitin bands formed in a counterelectrophoresis system.

The contractor is continuing to provide antisera specific for interspecies, gs-1 type antigen by two approaches: (1) purification of immunizing antigens and (2) through utilization of the time-sequential response of the immunized host, selection of a harvest time to correspond with the greatest differential between the interspecies gs antibody titer and the titer of other antibodies (notably gs-3 antibody). Antibody titer is being measured by both counterelectrophoresis and complement fixation. Studies in progress indicate that the immune response in swine remains specific for interspecies antigens for about 30 days.

Goats, swine, rats, and rabbits are being employed as hosts for antigens used for the continued production of oncogenic virus antisera.

Significance to Biomedical Research and the Program of the Institute: The reagents and test systems developed and produced by the contract are vital tools in cancer research. The project functions in close collaboration with SVCP research projects and is felt to be of very significant usefulness to the needs of the program.

Proposed Course: To continue development, characterization, and production of antisera and serological test systems.

Date Contract Initiated: June 2, 1963

Current Annual Level: $287,045

JOHNS HOPKINS UNIVERSITY (NIH 69-2008)

Title: Maintenance of a Flock of RIF-Free Chickens

Contractor's Project Director: Dr. Frederik B. Bang

Project Officer (NCI): Dr. W. Ray Bryan

Objectives: To maintain the small "closed" flock of leukosis-free White Leghorn chickens to supply fertile eggs for use in avian tumor virus studies and to continue development of a potential continuous chicken cell line.

Major Findings: The twelfth generation of the original flock is now in egg production. Eggs are used in cell culture and avian tumor virus studies at Johns Hopkins University.

Significance to Biomedical Research and the Program of the Institute: This flock supplied the birds used by Dr. Bang in his important studies on avian tumor viruses. There is no recognized continuing need for either this flock or cell line in the SVCP.

Proposed Course: Terminate

Date Contract Initiated: March 24, 1969

Current Annual Level: $22,308

LIFE SCIENCES, INC. (PH43-68-711)

Title: Production of Germfree and Reagent Grade Specific-Pathogen-Free Animals

Contractor's Project Director: Dr. Wendall M. Farrow

Project Officers (NCI): Mr. John P. Kvedar
Dr. W. Ray Bryan

Objectives: To produce both germfree and specific-pathogen-free (SPF) animals for research. SPF animals are maintained under environmentally controlled conditions which preclude intercurrent infection by pathogenic microorganisms or infestation by parasites and are referred to as "reagent grade" hosts.

Major Findings: The contractor's supply flock of SPF leukosis-negative White Leghorn chickens, housed in a 2600-square-foot area protected by a shower lock and recirculated, filtered air, now produces about 750 fertile

eggs/week. This quantity represents a major increase in production undertaken to meet increased program requirements.

Two smaller foundation flocks (designated as LSI-C68) of pedigreed chickens are maintained in separate SPF cubicles in the maximum security area. These pedigreed chickens are continually monitored for freedom from viral and other pathogenic agents and checked for egg production. Selective breeding has produced two flocks of barrier contained, reagent grade chickens with 75-80% fertility and 85-90% hatchability. The results of these efforts are reflected in the quality and quantity of the eggs and chicks from the production flock.

A production flock of Japanese quail consisting of 235 birds continues to supply fertile eggs to SVCP users at a rate of about 1100/week. In addition, it provides a steady input of 21 to 28-day-old quail to program. Representative sampling of aged quail in this production flock indicated that these birds were freed of the usual avian pathogens. This outbred quail flock is gradually being replaced by pedigreed, isolator-derived, cubicle reared quail. Within six months pedigreed birds will compose approximately 50% of the production flock.

An inbred pedigreed foundation colony of Balb/c mice free of all laterally transmitted viruses tested for continues to be maintained. Two random bred production colonies derived therefrom continue to supply certified SPF mice to certain SVCP investigators. In addition, a foundation colony of certified SPF NIH Swiss mice is being maintained as insurance against loss to program of this valuable stock.

Significance to Biomedical Research and the Program of the Institute: This contract serves as an essential supply of embryonated eggs and day-old chicks to contract NIH 69-93, which involves studies on Marek's disease as a model for herpesvirus-associated oncogenesis. It also provides other SVCP investigators with genetically and microbiologically well-defined laboratory animals. The advantage of having such animals is that oncogenic and suspected oncogenic viruses can be administered to them with a minimal danger of interference from other contaminating, adventitious microorganisms. Therefore, research can be carried out upon animals with a known and controlled viral flora, and cell lines can be derived from these animals which share this same advantage.

Proposed Course: This service-type contract for the production of germfree and reagent grade SPF animals will be continued, with the flexibility of being reoriented as rapidly as possible to meet changing needs of SVCP activities as they occur.

Date Contract Initiated: February 8, 1968

Current Annual Level: $416,806

UNIVERSITY OF LOUISVILLE (PH43-66-902)

Title: Preparation of Simian Foamy Virus Reagents and Antisera

Contractor's Project Director: Dr. Paul B. Johnston

Project Officer (NCI): Dr. Robert Holdenried

Objectives: To prepare and test reference reagents (virus and corresponding antisera) for the simian foamy viruses, types 1-7, and foamy virus from other laboratory species.

Major Findings: The seven types of simian foamy viruses and antisera against them have been prepared, packaged, and tested for homogeneity, potency, and purity. Although primary or subcultured rabbit kidney cells remain the only satisfactory "universal host cell" for the propagation of all seven types of simian foamy viruses, a normal rat kidney (NRK) cell line, received from Dr. George Todaro of NCI, has supported excellent growth of all foamy viruses except type 4. The NRK line was subsequently used to prepare 3 liters each of types 5 and 7 foamy virus which were shipped to Dr. Maurice Green.

In tests to determine relationships between the simian foamy viruses and viruses from other laboratory animals, it was found that inoculation of PRK or BHK-21/13 cells with Mason-Pfizer monkey virus (M-PMV) did not produce syncytia after prolonged incubation under conditions optimal for detecting syncytia of all seven types of foamy viruses. Antiserum against M-PMV was devoid of neutralizing antibody against foamy virus type 5. In addition, none of the seven foamy virus antisera neutralized feline syncytial virus.

Consultation and/or foamy virus reagents are being provided to other SVCP investigators on a regular basis.

Significance to Biomedical Research and the Program of the Institute: The simian foamy virus reagents will be used in the identification of viruses and viral antibodies in primates used for cancer research. The indigenous viruses of laboratory primates pose husbandry problems, in addition to contaminating test systems and complicating the attempts to recover oncogenic virus from tissues and tissue extracts. The specific antisera may also be useful in suppressing the growth of these adventitious viruses in primate tissue cultures.

Proposed Course: The packaged foamy virus reagents now in low temperature storage will be checked for titer stability at selected time intervals. This laboratory will also assist in the detection of foamy virus contaminates on a referral basis, as well as continuing to provide foamy viruses and antisera to SVCP investigators.

Date Contract Initiated: June 13, 1966

Current Annual Level: $22,000

MELOY LABORATORIES (NIH-72-3202)

Title: Murine Mammary Tumor Virus Studies

Contractor's Project Director: Dr. John E. Verna

Project Officers (NCI): Dr. Louis R. Sibal
Dr. Ray Bryan

Objectives: To propagate, concentrate, and distribute murine mammary tumor virus (MTV) for collaborating SVCP investigators; to perform immunological and biological assays for the detection and quantitation of MTV; to develop improved methods for the propagation and detection of MTV and MTV antigens; to conduct studies on the control of neoplasia in the susceptible murine host by vaccination with inactivated virus.

Major Findings: The primary purpose of this contract is the production of quality reagents for the study of the mouse mammary tumor virus system as a model for the further examination of the human breast cancer problem. The contractor is purifying MTV from the milk of C_3H mice by the combination of rate zonal and isopycnic centrifugation. Purified virus is employed in the following ways: (a) as a source of supply to various SVCP investigators, (b) as a reagent in the HA, HAI, and ID tests, (c) employed to produce MTV antiserum in rabbits and guinea pigs, and (d) used in cell culture experiments.

Purified virus and/or viral antisera and skim C_3H mouse milk have been sent to the following investigators: Dr. R. Gilden, Dr. G. Todaro, Dr. G. Smith, Dr. W. Yoklick, Dr. A. Gazdar, Dr. A. Rabson, Dr. D. Moore, Dr. P. Blair, and others.

Some additional studies that are associated with the contract include the serological testing of human mild and human sera as well as human and mouse tumor extracts and cell culture homogenates that are received through the Project Officer or that are generated through the developmental phase of this

contract. These samples are examined for the presence of MTV antigens or antibodies. Experiments are currently in progress which attempt to demonstrate the specificity of the reactions that have detected common or cross-reacting antigens or antibodies in human milk and sera. Complement fixation assay and protein analysis have been added to the capabilities of the MTV assay laboratory and serve to supplement the present assays.

A developmental phase of the contract is concerned with the establishment of an in vitro cell culture source of MTV. Some preliminary data have been accumulated which demonstrate that MTV synthesis does occur in mammary tumor cell cultures. The presence of hydrocortisone, prolactin, and insulin results in an increased amount of virus synthesis as determined by HA and HAI. Even though marked stimulation of virus synthesis is observed in primary cultures in the presence of prolactin, hydrocortisone, and insulin, the conditions under which the positive cells can be cloned to obtain a culture with a high percentage of virus producing cells still remains unresolved. Experiments which are designed to preserve and stimulate virus synthesis in the MTV positive cells are now in progress.

Significance to Biomedical Research and the Program of the Institute: Breast cancer is a leading cause of death from cancer among women. The finding of a virus, resembling a Type B RNA oncogenic virus of mice, in the milk of a significant number of women from high-risk breast cancer families strongly suggests a possible viral etiology for this disease. A major effort of the Special Virus Cancer Program will be directed toward determining the relationship of viruses to human breast cancer. This contract was established for the purpose of obtaining correlative information on the detection, isolation, and propagation of a murine mammary tumor virus, because this is the only available animal model system in which approaches to the study of viruses as a cause of breast cancer in many may be developed.

Proposed Course: Purified MTV, viral reagents, and mouse milk will continue to be supplied as needed by SVCP investigators. In addition, the biological and immunological methods developed in this laboratory will be used in systematic studies to develop further the mouse MTV system as a laboratory model for breast cancer virus studies in man. Greater emphasis will be placed on propagating this virus in tissue culture and on in vivo infection of cells in cultures. It is anticipated that the information gained from these studies will be applied to human breast cancer studies.

Date Contract Initiated: December 30, 1965

Current Annual Level: $688,212

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES (NIH-71-2116)

Title: Acquisition of Human Materials for Use in the Search for Transmissible Agents in Human Tumors

Contractor's Project Director: Dr. Yashar Hirshaut

Project Officer (NCI): Dr. Jack Gruber

Objectives: To gather sera and tissues from patients with tumors to be used in the search for tumor-specific antigens and human oncogenic viruses.

Major Findings: The tumor procurement program at Memorial Hospital for Cancer and Allied Diseases was established on March 1, 1971 under contract with the Special Virus Cancer Program. It operates as an independent administrative unit called the Tumor Procurement Center, but is closely affiliated with the Clinical Immunology Service of the Department of Medicine, Memorial Hospital. In the first 3 months of its existence, the administrative groundwork for the program was laid, a competent staff was hired, and arrangements were made for efficient tumor collection and data processing. Operations began on June 1, 1971 and since that time, nearly 5000 serum specimens have been collected, 591 surgical cases have been screened, 164 tumor samples have been gathered, and 69 effusions obtained. Numerous samples have been distributed to investigators in the SVCP, including Drs. Hidesaburo Hanafusa, David Yohn, Sol Spiegelman, Robert Gallo, Harry Eagle, and Anthony Girardi.

Significance to Biomedical Research and the Program of the Institute: In the last ten years, rapid progress has been made in the study of oncogenic animal viruses. Unfortunately, human studies have frequently been limited by the lack of suitable materials to be used in virus isolation and detection attempts. The procurement program at Memorial Hospital for Cancer and Allied Diseases in New York City provides cooperating investigators with sufficient numbers of specimens from tumor-bearing patients to permit them to undertake intensive studies of the possible viral etiology of human cancer.

Proposed Course: In the coming year, a modest expansion of the program is foreseen to take greater advantage of the extensive resources of Memorial Hospital. With the experience gained in the first contract year, it should be possible to service additional investigators. The close collaborative

relationship between the procurement program and participating investigators has assured that the materials provided are optimal for the needs of each laboratory. It is hoped that these associations will be strengthened in the future.

Date Contract Initiated: March 1, 1971

Current Annual Level: $95,000

UNIVERSITY OF MICHIGAN (PH43-65-639)

Title: Collection of Leukemia-Lymphoma Specimens

Contractor's Project Director: Dr. Chris J. D. Zarafonetis

Project Officers (NCI): Dr. Paul H. Levine
Dr. Ernest J. Plata

Objectives: To collect and distribute specimens and information from patients with leukemia or lymphoma.

Major Findings: The major efforts of the contractor have been divided between procurement of specimens, evaluation of special clinical situations, and computerization of the Simpson Memorial Institute Serum Bank. The first phase of the computerization program, which was undertaken to provide immediate and accurate information on the location and availability of specimens in the Serum Bank, was completed. The core data for 25,071 specimens have been keypunched and a program which interdigitates with PAC has evolved.

Over 4,000 serum specimens have been collected during the past year, along with various tissues from patients with breast cancer, American Burkitt's lymphoma, leukemia, Hodgkin's disease, reticulum cell sarcomas, lymphosarcomas, and malignant lymphomas. Recipients of these samples have included Drs. Spiegelman, Terasaki, Herberman, Levine, Gallo, Aaronson, Todaro, and numerous others within the SVCP.

Significance to Biomedical Research and the Program of the Institute: Availability of clinical specimens and pertinent information on the cases is paramount in the achievement of a major goal of the SVCP, i.e., to identify, rescue, characterize, and propagate a candidate human cancer virus. Large volumes of leukemic cells are necessary for the biochemical characterization of the polymerases present in these cells, and a large number of tissues will be necessary to keep up with the biochemical demand. In addition to helping meet this need, the contractor is also collecting a large number

of sera for the SVCP serum bank and has been able to meet new requests for a variety of specimens for SVCP investigators.

Proposed Course: Continuation as described.

Date Contract Initiated: June 21, 1965

Current Annual Level: $98,098

MICROBIOLOGICAL ASSOCIATES, INC. (PH43-66-914)

Title: Establish and Operate a BALB/c Mouse Colony

Contractor's Project Director: Mr. Wilbur Athey

Project Officer (NCI): Mr. Samuel M. Poiley

Objectives: To provide BALB/c mice for laboratory investigations supported by the SVCP, primarily for virus bioassays on Contract 43-67-697.

Major Findings: The contractor has provided the maximum numbers of mice that can be produced in 2,500 cages. All regulations of The Institute for Laboratory Animal Resources are followed carefully. Requests for animals based on age, sex, weight, suckling litters, or breeders, etc. have been consistently met.

Production under this colony has been increased to fully utilize the capabilities of half an animal building (1050 square feet) at Walkersville, Maryland. Production during the next year should yield 60,000 to 65,000 weanling mice plus the necessary pregnants for the program. This maximum yield will be possible only if the majority of mice are used at weanling age. Significant requirements for older aged mice will reduce the total number produced.

The results from the installation of a metering dispenser to acidify the water to a pH of 2.5 have not been conclusive but should show positive results during the next contract year. The serologic testing for a battery of murine viruses is scheduled on a quarterly basis as directed. At the last regular test, all samples were serologically negative to all viruses tested.

Significance to Biomedical Research and the Program of the Institute: The murine tumor viruses are being extensively studied as models for human cancer viruses. The availability of high quality BALB/c mice is important for assay of these viruses as well as for other studies in viral oncogenesis.

Proposed Course: Mouse production will be continued at the current level.

Date Contract Initiated: June 16, 1966

Current Annual Level: $64,000

MICROBIOLOGICAL ASSOCIATES, INC. (PH43-67-700)

Title: Development of Laboratory Animal Virus Diagnostic Reagents and Services

Contractor's Project Director: Dr. John C. Parker

Project Officers: Dr. Robert Holdenried (NCI)
Dr. Wallace P. Rowe (NIAID)

Objectives: To develop reagents and tests for the detection of murine and other laboratory rodent and cat viruses; to apply these and other tools in the determination of the importance of the indigenous viruses in experimental systems; to study means for elimination of viruses from laboratory animal populations. An additional collaborative study to assist in the characterization of the gene-dependent expression of murine leukemia was initiated in August 1971 and continues.

Major Findings: This contract project provides to the NCI a heavily used, highly skilled murine virus diagnostic laboratory. In the year ending September 30, 1971, 5,467 serological specimens were received and 52,580 tests performed. In addition, indirect tests (mouse antibody production) were performed on 116 specimens. The laboratory has the capability of performing serological test detecting infection with 32 known viruses or closely related groups of viruses.

To assist with the viral definition of cats to be used in cancer research, rapid diagnosis tests for 17 cat viruses have been developed and assayed for sensitivity. These serological tests involve either complement fixation or hemagglutination-inhibition procedures. Microneutralization assays were also developed for each of the cat viruses. These test systems are applicable to identification viral isolates or antibody.

Lymphocytic choriomeningitis (LCM) virus, which may cause serious disease in humans, continues to be of concern to research laboratory personnel using rodents. Collaboration studies revealed a significant incidence of infection in wild house mouse populations in Southern California where these mice are being utilized in a contract cancer research project.

A high incidence of LCM virus infection was also found in a commercial laboratory mouse production colony. The contract personnel assisted the producer in determining the extent of infection, preparing serological diagnostic reagents for use in another laboratory and in alerting mouse-using laboratories about the potential health hazard to their laboratory personnel.

Virus diagnostic reagents were prepared and certified for use on the in-house serological service program and research studies, for both the American Type Culture Collection and the World Health Organization virus reagent program, and for distribution on SVCP's request.

A natural history study of the mouse thymic virus, a herpesvirus, was initiated. With the development of complement fixation and fluorescent tests for this virus a major impediment to progress was overcome. The virus was detected in one of three mouse colonies examined to date. The effect of infection on immune functions particularly in relation to leukemogenesis is being investigated.

The preparation of monotypic homologous antisera in cats to 6 cat viruses was completed. The results of an investigation on the relationship of the cat picornaviruses will be presented by Dr. Parker at a WHO meeting on viral nomenclature.

Significance to Biomedical Research and the Program of the Institute: The virus diagnostic capabilities provide the NCI with the ability to monitor laboratory rodent and cat colonies and laboratory animal-produced viral reagents and tumors which have resulted in the production of highly characterized systems for cancer research. This contract provides assistance and guidance of particular importance for the detection of LCM in rodent systems. LCM virus, in addition to being infectious for humans, is difficult to detect. Significant contributions are being made to the knowledge of the natural history of several indigenous viruses of laboratory animals.

Proposed Course: Continue the rodent virus serodiagnostic service and develop a similar service for cat viruses. Improve the sensitivity and reliability of the tests. Apply the information developed to reduce and control viral infections in laboratory animal colonies and materials derived from animals.

Date Contract Initiated: April 10, 1961

Current Annual Level: $450,000

MONTREAL CHILDREN'S HOSPITAL (PH43-65-1020)

Title: Procurement of Normal and Leukemic Sera from Children

Contractor's Project Director: Dr. Ronald L. Denton

Project Officer (NCI): Dr. Paul H. Levine

Objectives: To obtain sera from a variety of pediatric oncology patients, family members, and controls for virologic study; to identify special cases for more extended workup.

Major Findings: Serum procurement during the last year included collections from 41 new cases of acute leukemia, solid tumor, 58 family members and 22 controls. 46 followup samples were obtained from previously studied patients. Among the 92 other specimens collected, special attention was given to a new American Burkitt's lymphoma patient, two patients with osteogenic sarcoma, a patient with malignant histiocytoses, and one with a congenital lesion (Birdman syndrome) associated with acute leukemia. In addition to the 1243 vials of serum and plasma that were transferred to the Flow Laboratory Serum Bank, the majority of the specimens collected by the contractor were sent to Dr. R. Gallo, Dr. S. Spiegelman, Meloy Laboratories, and Bionetics Research Laboratiries.

Significance to Biomedical Research and the Program of the Institute: This contract is one of the program's primary sources of serum from leukemic children and from suitable, normal controls. The increasing need within the SVCP for samples of this kind makes it essential that the supply be continued to satisfy research requirements.

Proposed Course: Continue to collect serum specimens, especially from selected leukemia patients, for identification of host factors associated with long-term survival.

Date Contract Initiated: September 24, 1965

Current Annual Level: $30,000

UNIVERSITY OF PADUA (PH43-68-1389)

Title: Collection of Human Tissue Specimens

Contractor's Project Director: Professor Giovanni Dogo

Project Officer (NCI): Dr. Robert H. Depue, Jr.
Dr. Charles W. Boone

Objectives: To establish fibroblast cultures from skin biopsies taken from inbred and isolated human donors and to provide these cultures to NCI for use in research programs.

Major Findings: Skin biopsies have been obtained from inbred and isolated populations in the Dolomite Mountains in Italy and have been grown in tissue culture. A sample of each culture has been sent to NCI; in addition, blood samples have been procured from each donor, and family trees going back to the fifth or sixth generation have been established for each individual. The contractor is presently using the geneological information to identify subjects belonging to family groups having a high incidence of neoplasia.

Significance to Biomedical Research and the Program of the Institute: The cell lines established from these skin biopsies will be used in a project to detect human oncogenic viruses *in vitro* and to determine the significance of the transformation test to oncogenesis.

Proposed Course: To collect and culture human skin biopsies as previously, along with genealogies.

Date Contract Initiated: October 27, 1964

Current Annual Level: $8,000

CHARLES PFIZER AND COMPANY, INC., (NIH-70-2080)

Title: Tumor Virus Research

Contractor's Project Directors: Dr. J. J. Oleson
Dr. Sami Mayyasi

Project Officers (NCI): Dr. Jack Gruber
Dr. W. Ray Bryan
Dr. Roy F. Kinard

Objectives: Provide research and services related to the isolation, production, purification, assay, and control of tumor viruses, including electron microscopy, tissue culture, and immunology applied to the study of animal and potentially oncogenic human viruses.

Major Findings: Recent advances have markedly increased the requirements of the SVCP laboratories for larger quantities and varieties of high grade, specifically prepared virus materials for biochemical, biological and immunological studies. New C-type viruses, of great interest and priority to the program, must be made in sufficient quantities for

in-depth studies. The contractor has responded by increasing production levels 30% to 600L/week, modifying a laboratory into a high containment production/research facility, purchasing additional centrifuges, hoods and other equipment and transferring personnel to this contract.

A total of 6,205 liters of fluids containing virus was produced these past 16 weeks of which 57% was mammary viruses and 32% was Rauscher leukemia virus.

The RD-114B sarcoma virus cell line, received late in December, has grown well and currently is being produced at 45 liters/week. The contractor plans future scale-up to 100 liters pending installation of new centrifugation apparatus for further purification processing. Preliminary virus growth and characterization studies have shown that several different human cell lines are susceptible to infection with this virus. These results encourage attempts to develop an assay for tissue culture infectivity.

Important new information and technology have been developed with the R-35 mammary tumor virus, concerning stability, purification, cell transformation, tumor cell and virus morphology, antigenic characterization, bioassay systems and biochemical characterization.

Comparisons of the reverse transcriptase (RDDP) activities and high molecular weight RNA content in virus concentrates after varied growth, harvest, and purification conditions now guide attempts to make high quality M-PM and Rauscher viruses for biochemical experiments. With some cell culture lines the RDDP content of virus produced has been shown to be a function of the culture transfer history.

Two new simian lymphoma and sarcoma viruses have been received and the contractor plans to produce limited amounts of each.

Substantial improvements in biohazard control have been achieved with the introduction of new operational procedures, equipment and personnel indoctrination.

Electron microscope services were provided for SVCP investigators and also supported the contractor's activities.

Significance to Biomedical Research and the Program of the Institute: Since its inception, this contract has provided support to individual investigators thereby making possible research which could not otherwise have been undertaken. The research conducted in the contractor's laboratories has largely been directed to improving the quality of material support to different research activities.

Proposed Course: The production of virus and cell materials in support of pertinent research will continue.

Date Contract Initiated: November 6, 1961

Current Annual Level: $1,685,821

ST. JOSEPH'S HOSPITAL (NIH 69-2074)

Title: Study of Human Sarcomas and Their Possible Viral Etiology.

Contractor's Project Director: Dr. Jeno E. Szakacs

Project Officers (NCI): Dr. Albert J. Dalton
Dr. Roy F. Kinard

Objectives: To find and supply fresh human sarcomas or other tumors which contain EM evidence of virus particles, and to attempt to establish cell cultures from some of these tumors.

Major Findings: Continuous tissue cultures established from human sarcomas collected from Tampa Bay area hospitals are being surveyed for virus particles by electron microscopy (EM). Of the eighty sarcomas collected during the year, forty-four cultures are now available for study which range from first to twentieth passage cultures. Each second passage is surveyed by EM.

During the latter part of the year, experiments were undertaken to induce chemically the appearance of virus particles in some of these cultures. At least one of the cultures thus treated has yielded virus particles, identification of which is currently underway.

Methods of tissue culture in the contractor's laboratory have been refined in order to permit the preferential cultivation of well-characterized tumor cells. Cloning and other new methods of handling the cultures were applied to this problem; in addition, immunofluorescent studies of the cultures were extended further.

A total of twenty tissue cultures derived from human sarcomas and 265 serum samples were shipped to NCI during the year. Serum collection, both for the sarcoma project and for Serum Bank projects, is continuing.

Significance to Biomedical Research and the Program of the Institute: This is an important project concerned with the search for viruses in human tumors. Extensive and careful

examination, by electron microscopy, of a large number of human tumors and cell cultures established from these tumors is essential in determining the viral etiology of cancer.

Proposed Course: All sarcoma cultures in the contractor's possession will be placed under chemical induction, and isolation and characterization will be attempted on all virus particles so obtained. The collection of sarcomas, case histories, and sera will continue. As volume increases, tumor tissues will be made increasingly available to SVCP investigators.

Date Contract Initiated: June 24, 1969

Current Annual Level: $108,315

SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION (NIH 69-2011)

Title: Housing and Maintenance of a Chimpanzee Colony

Contractor's Project Director: Dr. Seymour S. Kalter

Project Officer (NCI): Dr. Roy F. Kinard

Objectives: To supply young chimpanzees to SVCP investigators.

Major Findings: The animals maintained under this contract have been in generally good health during the year despite the occurrence of two deaths and several individual illnesses. Five infants (three males, two females) were born during this period, one of which, a female, was sent to Baylor Medical School along with an infant male and an infant female born late in 1970.

The chimpanzee colony now comprises the following animals: six breeding age females, one breeding age male, one juvenile male, two juvenile females, three infant males, and two infant females, for a total of 15 animals.

Significance to Biomedical Research and the Program of the Institute: The chimpanzee now appears to be the laboratory animal most similar to humans, biochemically and immunologically. Newborn chimpanzees are particularly useful in determining susceptibility to suspected human cancer viruses because their resistance to virus infection is very low. This is the only source of newborn chimpanzees for the SVCP.

Proposed Course: The chimpanzee colony will be maintained as before and newborn animals will continue to be supplied to investigators within the SVCP.

Date Contract Initiated: April 25, 1969

Current Annual Level: $25,000

UNIVERSITY LABORATORIES, INC. (PH43-66-1133)

Title: Production of Oncogenic Viruses and Antisera

Contractor's Project Director: Dr. Eugene H. Bernstein

Project Officers (NCI): Dr. Robert Holdenried
Dr. Robert Bassin
Mr. Gary Armstrong

Objectives: Production of leukemia and sarcoma viruses and antisera.

Major Findings: Within the year immediate SVCP needs for MSV(M), harvested from BALB/c mouse tumors, and the Moloney leukemia virus (I.C. strain derivation), harvested from BALB/c mouse spleens, were met and production was suspended. These viruses, in storage at the Flow Laboratories repository, are issued upon request to research projects. The production of mouse antiserum to MLV was also completed. This serum has a highly specific neutralizing titer for MLV. The production of Rauscher leukemia virus, which is harvested from the plasma of infected mice, has been initiated and is proceeding at the rate of about 400 ml. per month. Virus particle count by electron microscopy (EM) is 10^7 particles/ml., but assay of the virus on S+L- cells yields a titer of 10^3-10^4 focus-forming units/ml.

Cat leukemia virus (F-422 of Rickard) production was initiated in a continuous line of thymus cells and continues at the rate of about 4,500 ml. of culture fluid per month. Examination of the fluid by EM reveals a particle count of about 10^{10} particles/ml.

Several avian viruses are being produced in cell cultures. Rous sarcoma virus (Prague strain) is produced in the largest volume, about 25 liters of culture fluid per week. After being pelleted and resuspended, the virus is issued at 100X its original concentration. Production of Rous-associated virus 7 (RAV-7) terminated in December and RAV-2 is now being produced in its place. The production rate is about 2 liters per week.

Significance to Biomedical Research and the Program of the Institute: The supply of highly standardized oncogenic viruses and antisera produced by this contractor has been

extensively used by SVCP researchers and is essential to the continuation of many important research projects presently being carried out in the program.

Proposed Course: The contractor has largely shifted from producing virus in animals to cell culture propagation. Production of needed strains of oncogenic viruses and their antisera will continue in volumes necessary to meet SVCP research needs.

Date Contract Initiated: June 4, 1962

Current Annual Level: $322,140

WOLF RESEARCH AND DEVELOPMENT CORP. (NIH 71-2270)

Title: Computer Services

Contractor's Project Director: Dr. William Wells

Project Officers (NCI): Dr. Deward E. Waggoner
Mr. Theodore Weiss

Objectives: The major objective of this contract is the implementation of a computerized central inventory system for the various resources of the SVCP. The system now being installed embraces a number of institutional repository subsystems contributing to the central base in the Program Analysis and Communications Office (PAC). Each computerized subsystem is used at a given resource repository to inventory the items produced or stored at that location. Since the types of resources at the various resource banks differ in kind, the subsystems all differ to some extent. They are, however, all designed to contribute compatible information to the central system in PAC, thus forming the base for a program-wide central inventory and control.

The resource bank subsystems are also used at storage sites for controlling materials in functions unique to each institution, and this contributes to the detailed differences. Some of these secondary functions include catalog production, local inventory, and retrieval of clinical information.

Major Progress: A thorough systems analysis, documentation, and integration of all ongoing computer data processing of the serum bank operations in PAC was compiled and reproduced in a single manual (PAC I). In addition to its use as a compact operating manual, this served as a security measure, insuring future continuity of operations with the possibility of personnel change in a complex data milieu.

The serum bank inventory system was then redesigned to include all other human specimens (especially tissue and cell lines). It was further expanded to include a wide array of clinical, laboratory, and demographic information on specimen donors, parameters expected to be useful in the selection of specimens and in interpreting results of virus laboratory testing. Extensive documentation of the new and expanded system (PAC II) was reproduced as an operating manual. While the compact computer systems therein will have greatest use in managing the Washington area specimen banks, they are designed to adapt to any institution contributing to the SVCP human resources. Compatibility of information codes and operating format between SVCP Bethesda and cooperating institutions is an integral principle of PAC II.

Wolf Research and Development has completed, in collaboration with SVCP personnel, the following work in repository subsystems:

1. University of Michigan. Management studies were conducted for operation of the serum bank at Simpson Memorial Institute. Systems were designed, personnel trained, and descriptive data on 26,000 human specimens added to the PAC serum bank inventory.

2. Naval Biomedical Research Laboratory. Systems were studied, data forms prepared, and a proposal for automation of the cell culture repository submitted.

3. M. D. Anderson Hospital. Conversion of the data concerning the specimen repository to the new PAC II central inventory format is underway.

Significance to Biomedical Research and the Program of the Institute: The necessary expansion of the inventory of viruses, sera, tissue cultures, human specimens, and other materials used in cancer research makes it vital that close control be exercised over these resources. Computerization of the inventory will eventually make it possible for the Office of Resources and Logistics to rapidly obtain information necessary to determine availability, location, quantity, etc. of all resources within its jurisdiction, thereby permitting rapid response to the needs of the program while avoiding resource excesses or shortages.

Proposed Course: The contractor will extend and refine the Central Inventory System. Efforts will include the implementation of the Query capability and the development of a program to select control specimens matched to the characteristics of selected study specimens. Work on subsystems will include: addition of further data from M.D. Anderson to the

NCI data base; proposal and implementation of a system for Memorial Hospital (N.Y.); addition of data on reagent production from Huntingdon Research Labs.; and integration of the NBRL system into the NCI system when funded.

Date Contract Initiated: May 3,.1971

Current Annual Level: $127,300

BIOHAZARDS CONTROL AND CONTAINMENT SEGMENT

Dr. Alfred Hellman, OASDVO, DCCP, Chairman

Mr. William Emmett Barkley, OASDVO, DCCP, Vice Chairman

THE DOW CHEMICAL COMPANY (PH 43-65-1045)

Title: Research and Development of Biohazards Containment Facilities

Contractor's Project Director: Mr. Cyril B. Henke

Project Officer (NCI): Mr. W. Emmett Barkley

Objectives:

1. In collaboration with the NCI Office of Biohazards and Environmental Control, the contractor performs Biological Safety and Environmental Control surveys of SVCP contractor operations to evaluate laboratory practices, safety equipment and facilities and to assess the effect of contractor operations on laboratory safety and environmental quality.

2. The contractor assists the Office of Biohazards and Environmental Control in the preparation and dissemmination of safety equipment specifications, facility design criteria, operations guidelines and safety procedures. The contractor also prepares engineering design drawings and specifications for containment systems required to meed specific program needs.

3. The contractor operates a safety equipment certification program to assure safe operation of SVCP safety and containment equipment.

4. The contractor assists the Office of Biohazards and Environmental Control in the review of plans and specifications for SVCP renovation and new facility construction projects.

Major Findings: The contractor participated in ten biological safety and environmental control surveys and has developed significant recommendations to improve the environmental quality of SVCP laboratory operations. Survey follow-up activities helped to eliminate potential safety and environmental control

problems experienced by a few of the contractors surveyed. The following examples highlight these activities: (1) containment systems were designed to eliminate potential hazards associated with oncogenic virus production, (2) recommendations for improved safety operation of the K-II centrifuge were developed, (3) recommendations for improving quality control practices of virus production activities were developed, (4) certification of in-use biological safety equipment was performed at the majority of survey sites.

The contractor assisted NCI in the development of minimum standards for biological safety and environmental control.

Significance to Biomedical Research and the Program of the Institute: This contract contributes biological safety and environmental control expertise to the SVCP. This expertise is used to improve the quality and safety of the cancer research laboratory environment. The contractor functions as an integral part of the NCI Office of Biohazards and Environmental Control.

Proposed Course: The contractor will continue to provide technical assistance to the SVCP contractors on problems of environmental control, personnel safety and product protection. The contractor will participate on approximately twenty-five Biohazard Safety and Environmental Control surveys. Plans for expanding the contractor's engineering design and review support activities will be initiated this year.

Date Contract Initiated: June 25, 1965

Current Annual Level: $200,000

OHIO STATE UNIVERSITY (PH43-65-1001)

Title: Biohazard Control and Containment in Oncogenic Virus Research

Contractor's Project Director: Dr. D. Yohn

Project Officers (NCI): Dr. A. Hellman
Dr. A. K. Fowler

Objectives: The purpose of this research program is to elucidate the possible hazards to man and animals from exposure to oncogenic viruses and their infectious nucleic acids. In addition the possibility that animal hosts are able to respond immunologically to their homologous oncornaviral antigens is being investigated and efficacy of various vaccine preparations is being tested.

Major Findings: All the virus parenteral and aerosol experiments have been completed. Three of eight groups of animals exposed to infectious nucleic acid remain in experiment. These include: 137 Swiss mice injected subcutaneously, 102 newborn and 102 thymectomized weanling mice exposed by the aerosol route, and 19 newborn and 82 weanling thymectomized PD_4 hamsters also exposed to an aerosol of infectious nucleic acid. All the remaining animals have been necropsied, gross lesions examined histologically, and terminal sera from the last groups are currently being tested by immunofluorescence for the presence of SV_{40} T-antibody. In the parenteral studies we have demonstrated that infectious SV_{40} DNa prepared from our semi-purified virus is oncogenic and that the subcutaneous route is more sensitive than the intracerebral route for challenge with either virus or nucleic acid. There were, however, fewer tumors in animals injected with infectious nucleic acid than those receiving whole virus. No tumors have appeared in the mice injected with SV40 infectious nucleic acid. No new tumors have developed in the aerosolized hamsters and mice.

In general, all the groups of hamsters and mice show evidence of infection by the presence of SV_{40} specific antibody. The control hamsters and mice are negative. All the tumor bearing animals in the parenterally injected groups as well as some non-tumor bearing animals have T-antibody.

Feline Leukemic Horizontal Transmission:

1. Intranasal transmission - The experiments demonstrating that feline leukemia is transmissible by a single intranasal inoculation of neonatal kittens are completed. One of 4 gnotobiotic kittens inoculated intranasally with FeLV in a final experiment to corroborate previous data has died of lymphosarcoma at 397 days of age. The remaining 3 cats are alive and free of clinical disease at 45 days of age.

Feline Virus Vaccine:

1. Immune reactivity of cats - This portion of the study, the definition of the immune response of the normal cat and cats with feline leukemia, was begun under the concept that the understanding of the pathogenetic mechanisms in feline leukemia, including response to an inactivated virus vaccine, would be aided by such knowledge. The objectives included identification, separation and purification of the immunoglobulin classes of the cat and quantitation of these classes in normal and leukemic cats of various ages. Also, humoral and cellular immune response would be evaluated following injection of sheep red blood cells (rbc) and application of allogenic skin grafts respectively to test for possible immunodepression in the leukemic cat. Finally, kidneys were to be evaluated by immunofluorescence for deposition of feline globulins suggesting immune complex deposition.

   IgG has been isolated from cat antiserum to sheep rbc.

   IgM separation has been accomplished using preparative ultracentrifugation and molecular sieve chromatography. Pools of saliva and tears from several cats stimulated with pilocarpine have been collected and concentrated for IgA separation and purification.

2. Preleukemic disease and immunosuppression - This investigation was designed to determine the sequential histologic alterations in lymphoid tissues, and bone marrow of preleukemic cats and to correlate these data with alterations in cell-mediated immunity. Twenty specific - pathogen-free (SPF) cats have been inoculated with feline leukemia virus. All cats inoculated with this viral stock can be expected to develop lymphosarcoma by 120 days of age. Twenty uninoculated control SPF cats serve as age-matched controls for the study. Striking thymic atrophy is manifest at 5 weeks of age at which time the mean thymus weight of preleukemic cats is 18% of control. Atrophy of the thymus is associated with a marked deficiency in cell-mediated immunity. FeLV-infected cats evaluated thus far (from 5 to 11 weeks of age) have significantly impaired capacity to reject cutaneous allografts from the same donor. Allograft rejection is still incomplete at 21 days post grafting.

   The onset of lymphosarcoma occurs at 8 to 10 weeks of age and is manifest by appearance of significant numbers of immature lymphoid cells in the bone marrow and by mesenteric lymphadenopathy. Large lymphoid cells accumulate initiatly in the deep cortex and proximal medullary sinuses of the mesenteric lymphodenopathy.

Data collected to date support the working hypotheses that 1) thymic atrophy and impaired cell-mediated immunity precede the onset of feline lymphosarcoma and 2) lymphosarcoma cells may originate in the bone marrow where they can be detected at or before the onset of the characteristic lesions of lymphosarcoma in lymphoid tissues. These manifestations may prove to be important early signs of the disease. They may permit a rapid preliminary diagnosis, therefore accellerating the evaluation of treatments such as vaccination, etc.

3. Vaccine development and evaluation - Objectives and experimental outline-killed virus vaccines prepared against the feline leukemia and sarcoma viruses are being analysed to determine their effectiveness as a means to prevent neoplastic disease in experimentally challenged cats. Results of this study may yield information concerning the feasibility and possible use of oncogenic virus vaccines in other species including man.

   Evaluation of vaccine effectiveness is being determined in vivo by challenge with oncogenic sarcoma virus preparations and in vitro by neutralization of observed feline sarcoma virus cytopathic effects.

Significance to Biomedical Research and the Program of the Institute:

Knowledge as to the hazard associated with virus and infectious nucleic acid transmission and crossing of species barriers is very important in the evaluation of risk where working with tumor virus and their nucleic acids. The development of a proto-type vaccine (feline) against a tumor virus in a random bred animal population will permit one to assess the feasibility of using such prophylactic measures in the control of human malignancy that possibly is induced by virus. The rather high natural incidence of such an etiologically associated disease in the cat makes this a very excellent model, which may be used as a human simulant. Control of this disease in the feline would suggest that it is feasible to accomplish this in man if a human tumor virus of sufficient range were found. Methods of extracting, processing and utilizing antigens from such viruses, which could be certified to be free from any genetically transmittable information would be a significant and very important step in permitting the licensing of such a future vaccine.

Proposed Course: In order to develop a model system to study the susceptibility of a host to concurrent infection and cross infection, the cat model is being developed. We plan to study this animal as one would humans on chemotherapy, in order to determine his capacity for antibody synthesis, response to chemotherapy, enhancement of malignancy by immunosuppression and look at the significance of hormonal imbalance in the development of malignancy. Both cellular and humoral immunologic responses will be investigated.

Date Contract Initiated: June 22, 1965

Current Annual Level: $257,570

NAVAL BIOLOGICAL LABORATORY (FS-57)

Title: Studies of Environmental and Physiological Factors Influencing Virus-Host with Interaction

Contractor's Project Directors: Dr. R. L. Dimmick
Mr. M. A. Chatigny

Project Officers: Dr. A. Hellman
Dr. A. K. Fowler
Mr. W. E. Barkley

Objectives: This contract has three objectives, they are:

1. Virus laboratory hazards evaluation. The objective of this section of the proposal is to evaluate the extent of possible hazards involved in biochemical and biophysical procedures used in virus-tissue culture laboratories.

2. Studies on environmental effects on physical and biological characteristics of viral aerosols. The objective of this section of the proposal is to provide survival data of both "model" and oncogenic viruses as related to environmental parameters (e.g. temperature, RH, RH changes, and trace chemicals - decontaminants) for use in Section 1, and to evaluate the importance of end-spectrum (0.1 to 0.5 mμ) (5 to 15 mμ) particles on virus-host interaction considering both the hazard to humans and animals and the potential for cross contamination.

3. Host-virus interactions. The objective of this section is to evaluate the effect of selected stress situations (physiological as by hormonal imbalance, immunological as by concurrent infection or biochemical, as by exposure to injurious chemical vapors of aerosols) on induction of viral disease or cancer in situ, and to evaluate the role airborne particle size might play in such interactions.

Major Findings:

1. Virus laboratory hazards evaluation. Preliminary data shows that use of tracers other than actual oncogenic virus will yield information equivalent to virus-data, and that use of such tracers will increase productivity.

   We have completed our test of a "Branson" sonic oscillator. Results substantiate the concept that a physical tracer can be effective.

   Initial tests have been made with an angle head centrifuge rotor, at 0 to 5000 rpm. The regular seal was intact and the rotor was filled with a suspension containing 10^8 bacteria/ml. The output was greater than 2.4×10^3/ft^3/min, but there were no particles

collected by an Andersen sampler in the 1 μ size range; the majority were 8 μ or larger. We are using this rotor to simulate the possible function of the zonal while we establish appropriate sampling techniques.

2. Studies on environmental effects on physical and biological characteristics of viral aerosols. Stability of the simian virus SV-40 has been tested at 7 values from 5 to 90% relative humidity (RH) and at 70°F and 90°F. At 70°F there was practically no loss in viability; at 90°F, in the range of 45 to 60% RH less than 0.1% remained viable after 60 minutes.

3. Host-virus interactions. Using tritium labeled estradiol, we have shown in a preliminary experiment that the respiratory dosage of estradiol calculated by atomizer output, air flow rate, and Guyton's formula (breathing rate for mice = 1.25 ml/gm/min) yielded a substantially correct value.

   The effective dilution ratio $\frac{\text{Activity in mouse lung}}{\text{Activity/ml in atomizer}}$ was 12.6×10^{-5}. The calculated dosage was 4.2×10^{-8} gms/mouse; the value calculated by the ratio was 4.7×10^{-8} gms/mouse. This dosage caused an increase in weight of the uterus of ovarectomized mice, acted as a group specific antigen activator, and was not transmitted to cagemates.

Significance to Biomedical Research and the Program of the Institute:

An understanding of the survival and clearance rate for virus aerosol will allow the development of a rational and hopefully less expensive means for control of cross infection. Similarly development of mathematical models will permit the more precise evaluation of facilities, on the basis of risk. Transmission of chemicals that are found in the environment, which have been demonstrated by Hellman and Fowler to induce activation of tumor virogenic markers (g.s. and reverse transcriptase), make an understanding for their potential to activate such markers by the respiratory route very important in the evaluation of risk either as a primary or co-inducing factor.

Proposed Course: We are currently evaluating the output of blendors using fluorescein dye. The aerosolized dye is collected in AGI impingers and measured spectrophotometrically. Additional equipment or techniques to be tested are:

1. Centrifuge
2. Culture shaker
3. Mechanical mixer
4. Dropping liquid on surface
5. Mixing with a pipette
6. Dropping a flask

In instances where aerosol output is too dilute to measure by fluorescein output, we will employ the NBRL microaerofluorometer, supplemented by biological tracers.

At present, test units are being held in the smallest possible space to ensure maximal collection efficiency. We intend to test a limited number of the above in a large volume (room) where ventilation and gross air patterns can be reasonable controlled.

We are concerned that our present nomograph is too complex for convenient use. We must, however, ensure that the range of each variable includes all possible operating conditions. We will investigate the question of whether, in a given case, the assumption of a uniform concentration in a room compared to the assumption of limited spaces with unequal concentrations will yield exposures that are equivalent within desired limits of accuracy.

A thermal precipitator is being constructed. It will be used to collect particles in the sub-micron range.

Date Contract Initiated: March 1, 1971

Current Annual Level: $100,000

SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION (NIH-71-2348)

Title: Study of Latent Virus Infection and Transmission

Contractor's Project Director: Dr. S. S. Kalter

Project Officer (NCI): Dr. Alfred Hellman

Objectives: It is the purpose of this contract to study various aspects of the role of latent virus infections of laboratory animals and cultures of their organs as a source of contamination of experimental materials, laboratory personnel and vaccines. As a part of these studies the rate of inactivation of virus infectivity and oncogenicity by heat and ultraviolet light will be determined for several viruses in the extra- and intracellular state. The viruses selected for study are of interest because of their demonstrated oncogenic potential, ability to maintain a persistent, inapparent infection of cell cultures and the physical state of their genome.

The possible transmission of cancer by inhalation of tumor cells will be studied in mice and hamsters by inoculation via the intranasal route with tumor cell suspensions and aerosols.

The role of antiserum in establishing persistent infections will be studied.

Major Findings: Studies on the intracellular inactivation of H. hominis types 1 and 2 at 4°C, RT, 37° and 56° have continued. During the last report period intracellular (Vero) virus had persisted at 4° for 16 days. This experiment was continued to 42 days with little, or no, drop in titer for either virus. Data collected on thermal and U.V. inactivation of HSV 1 and 2 indicated intracellular virus was inactivated thermally more slowly than extracellular virus, but U.V. inactivation occurs about the same rate in both states. Emperical observations suggest cell clumping, pH, medium composition and cell type are factors which influence reproducibility of results from sample and laboratory to laboratory. U.V. irradiated HSV 1 and 2 with infectivity destroyed have been inoculated into hamster embryo monolayers in a preliminary attempt to induce cellular transformation. After 7 weeks no changes have been noted. C_3H mouse tumor being carried by inoculation of the tumor cell suspension into the leg muscle of C_3H mice has been studied for its ability to induce tumors by the intranasal route. A suspension of 10^6, 10^5 and 10^4 cells per 0.02 ml was prepared. Approximately 0.01 ml of this suspension was inoculated into 2 week old C_3H mice by dropping onto the external nares and allowing it to be inhaled. All mice became ill and died or were sacrificed in a moribund state by the end of 3 weeks. Lung material from these animals was inoculated intramuscularly into other C_3H mice for passage and processed

for histopathology. Tumors were not grossly obvious on the lungs. Histopathological observations are not completed.

Four perinatal baboons were inoculated with Feline Leukemia Virus (Rickard Strain) received from the Project Officer by way of Virgo Reagents. No disease was noted in any of these animals and they were subsequently challenged with Tween 80 - Ether treated Feline Leukemia Virus antigen by the subcutaneous and intramuscular route. No viral antibodies have been detected in sera from these animals.

Significance to Biomedical Research and the Program of the Institute:

An understanding of whether latent virus is present in certain animal cell cultures permits one to evaluate the feasibility utilizing such a culture for propogation of virus for the development of vaccines. Similarly an understanding of how to make latent virus express itself will shed light into the whole question of transmission of genetic information and what factors stimulate the packaging of such information into whole virus. A knowledge of the physical factors necessary for activation and inactivation of tumor virus will provide a more rational approach to investigator protection.

Proposed Course: More detailed studies of the HSV 1 and 2 U.V. inactivation are planned to determine the influence of cell culture and state of intracellular virus on rate of inactivation. Thermal inactivation studies will be completed. Feline tissue explants will be started to determine latent virus in SPF cats. Respiratory inoculation with C_3H tumor cells and virus particles will be studied in more detail. A collaborative effort using primates and endocrine activation of tumor virus expression is being initiated as yet another method for detection of non-expressed virus information.

Date Contract Initiated: June 3, 197[illegible].

Current Annual Level: $57,400

UNIVERSITY OF MINNESOTA (NIH-NCI-72-2066)

Title: Development of Short Courses on the Principles of Biohazard and Injury Control for the Biomedical Laboratory

Contractor's Project Director: Prof. G.S. Michaelsen

Project Officer (NCI): Mr. W. Emmett Barkley

Objectives:

1. The University of Minnesota is responsible for the development of short courses on contamination control, biological, chemical and physical safety for biomedical laboratory personnel. Detailed training manuals, including lecture notes, literature references, tables, figures and laboratory exercises are to be prepared.

2. Four courses are to be presented annually to scientific personnel engaged in oncogenic virus research.

Major Findings: A course schedule, including approximately 18 topics and 3 laboratory sessions, has been developed. Lecturers for these topics have been selected.

The first course is scheduled for June 12-16, 1972 at the University of Minnesota. The remaining three course presentations will occur during the second half of the contract year. The course dates and location for the remaining three presentations have been selected and confirmed.

Significance to Biomedical Research and the Program of the Institute: This contract will provide an opportunity to scientific investigators and laboratory technicians engaged in cancer virus research to learn the fundamentals of laboratory safety and environmental

control including the correct usage of biological safety hoods, the adequacy of protective clothing and other personal protective devices, the role of disinfection and sterilization techniques and the principles of biological, physical, chemical and radiological hazard control.

In addition, course materials developed under this contract will be made available to the safety office of the Center for Disease Control, Atlanta, Georgia and to other appropriate safety groups in the biomedical community. These materials will make it possible for safety organizations to provide excellent safety training opportunities for all biomedical research personnel.

Proposed Course: The contract was initiated in December, 1971. The proposed course is to present four courses during the contract year to investigators and senior technicians in the SVCP. Two courses will be presented in Minneapolis and two at other locations corresponding to high density SVCP contract areas.

Date Contract Initiated. December 10, 1971

Current Annual Level: $105,000

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL AT DALLAS (NIH-71-2135)

Title: Biohazards Information Gathering Center: Surveillance of Laboratory-Acquired Infections and Accidents

Contractor's Project Director: Dr. S. Edward Sulkin

Project Officer (NCI): Dr. Alfred Hellman

Objectives: (1) To gather information concerning laboratory-acquired infections and accidents by the use of questionnaires and personal contact; (2) to make available information concerning the hazards of working with infectious agents; (3) to assemble information concerning techniques and equipment which would tend to minimize this hazard and (4) to prepare a continually updated guide for dealing with various aspects of this problem.

Major Findings: No progress as yet under this contract, contractor has had difficulty in getting program initiated.

Significance to Biomedical Research and the Program of the Institute: By becoming aware of the problem, as defined by past experience, it is hoped that work with newer agents, particularly oncogenic viruses, can proceed with a greater chance of protecting the safety of personnel involved.

Proposed Course: This laboratory will continue to serve as a clearing house for cases of laboratory-acquired infections and to encourage investigators to report instances of infections acquired in the laboratory. A follow-up of a questionnaire submitted over 10 years ago will be circularized to those working with oncogenic agents.

Date Contract Initiated: May 10, 1971

Current Annual Level: $12,026

SOLID TUMOR VIRUS PROGRAM SEGMENT

Dr. Robert J. Huebner, VCB, DCCP, Chairman

Dr. James T. Duff, VCB, DCCP, Vice Chairman

CALIFORNIA STATE DEPARTMENT OF PUBLIC HEALTH
(PH43-NIH-NCI-E-68-997)

Title: Role of Oncogenic Viruses in the Causation of Cancer in Man and his Domestic Animals

Contractor's Project Director: Dr. Edwin H. Lennette

Project Officer (NCI): Dr. James T. Duff

Objectives: To apply the newer knowledge of the nature of RNA viruses to the study of neoplasms of animals and man.

Major Findings: (1) Viral genome rescue experiments: Several approaches are being explored in attempts to rescue infectious Type C viruses from nonviral producing cell lines which have been established in this laboratory from tumors of cats, dogs, and humans. These include treatment of the cultures with mitomycin C, BrdU, IdU, x-irradiation, super-infection with infectious Type C viruses, co-cultivation with normal "susceptible" cells, or combinations of these procedures. To date the results of these experiments have been negative. (2) Experiments with anti-thymocyte serum (ATS) treated mice: ATS treated Swiss mice have produced recognizable adenocarcinomatous structures when minced tumor preparations from two of four human colon carcinomas were transplanted within two days after surgery. No tumors when third passage in vitro cultured cells from the same tumors were used in the ATS treated mice. C57/Leaden mice have been bred and have proven susceptible to HeLa cell tumor formation when treated with ATS. (3) Primate tumor induction experiments (in collaboration with Dr. Melnick at Baylor University): Baboon testis cells have been transformed in vitro by both the ST and GA strains of feline sarcoma virus (FeSV). Following transformation by either virus, the cells became sarcomagenic for ATS treated mice. These cells have been injected into the original cell donor baboons, and the animals are under observation for tumor development and anti-FeSV antibody production. (4) Feline gs-1 antigen studies: Feline gs-1 antigen purified by electro-focusing was inoculated into two guinea pigs to produce antiserum. Both guinea pigs responded with high CF titers and also showed only one precipitin line in immunodiffusion tests using crude ether-treated FeLV as antigen. Low titered reactions against normal cat cell antigen and fetal bovine serum were removed by absorbing with normal cat cells grown

in cell culture and by utilizing insolubilized fetal bovine serum which had been cross-linked with glutaraldehyde as an immunoabsorbent. (5) Indirect fluorescent antibody studies: Preliminary work has begun on attempts to localize feline gs-1 antigen in cells utilizing the indirect fluorescent antibody technique. The cells first used were both dog and cat cell lines which were chronically infected with FeLV and their uninfected counterpart as controls. In every case tested, so far, both guinea pig sera described above showed bright specific staining in the cytoplasm of only the cells infected with the virus, the uninfected controls remaining negative. (6) Virus in RD 114 cell line: The indirect ferritin-labeled antibody technique was applied to RD 114 cells to determine if the virus in RD 114 cells shared a common surface antigen with the feline leukemia-sarcoma viruses. The application of XD25M serum (antibodies to feline leukemia-sarcoma virus antigens) resulted in ferritin-tagging of the viral particles in the feline leukemia virus infected RD cell lines but did not show tagging of the viral particles in the RD 114 cell lines. (7) Type C virus on erythrocytes: The sequence of events in the development of feline Type C virus on the plasma membrane of erythrocytes has been elucidated in electron micrographs. Particles were observed in various stages of development, indicating that an erythrocyte can retain the necessary information for viral replication. (8) Feline syncytium-forming virus studies: Experiments have been completed on the growth of feline syncytium-forming virus. New infectious virus is produced by 20 hours post infection (PI) while new virus antigen can be detected at 12 hours PI using the fluorescent antibody technique. Syncytium began forming between 12 and 14 hours PI. (9) Focus-forming assay of feline sarcoma virus on beagle embryo cells (NBE3): Both the ST and GA strains of FSV can be grown and assayed on cultures of a normal beagle embryo cell (NBE3). The most sensitive titrations have been obtained on cells between the 30th and 50th passages. The FSV pools produced contain an excess of nontransforming (helper) virus as was shown in cell cultures inoculated with virus dilutions beyond the focus-forming endpoint (usually 10^{-3}).

Significance to Biomedical Research and the Program of the Institute: These studies are a part of a comprehensive field program on the etiology of cancer in man and his domestic animals being carried out as a collaborative effort between the California State Department of Public Health (NIH-NCI-E-69-87), the University of California (Naval Biomedical Research Laboratories, PH43-NIH-NCI-E-63-13), the University of Southern California and Los Angeles Children's Hospital (PH43-NIH-NCI-E-68-1030), Stanford University (NIH-NCI-E-69-2053), and other contract programs, including

in-house projects under VCB. To a large extent, the success of these programs depends on the acquisition of fresh human and animal (pet) cancer materials, cell lines derived from them, and sera from persons associated with pets with cancer. This group has responsibility for developing diagnostic techniques for feline Type C viruses and applying them in studies of the natural history of the cat virus for the purpose of applying what is learned to the natural history and etiology of human cancer. A major new objective will be to carry out fluorescent antibody studies of human tumor cells to study the possible interactions of human tumors with the RD 114 virus. Also, the development of methods of replicating human tumor cells in animals and of detecting Type C virus expression in them.

Proposed Course: (1) Continue to obtain cats and dogs with malignancies from local veterinarians in order to study their immunological relationship. (2) Continue to establish cell cultures from human tumors to study their tumorigenicity in ATS treated mice for the purpose of (a) verifying that they are tumor cell lines instead of the usual fibroblasts and (b) trying to "switch-on" human Type C virus by in vivo passage similar to the switch-on which occurred in RD cells on passage through a cat.

Date Contract Initiated: June 24, 1968

Current Contract Level: $227,715

CALIFORNIA STATE DEPARTMENT OF PUBLIC HEALTH (NIH-NCI-E-69-87)

Title: Human-feline Cancer Household Study

Contractor's Project Director: Dr. Robert Schneider

Project Officer (NCI): Dr. James T. Duff

Objectives: To determine if a significant etiological association exists between human and feline cancer using a retrospective study of households in which a malignant cancer has been diagnosed in a cat, and concurrently to look for and test the significance of apparent horizontal transmission of lymphoma virus from cat to cat.

Major Findings: The field and coding phases of the Animal Population Survey for Alameda and Contra Costa Counties have been completed. Of 31,165 valid households, 26,940, or 86.4%, were interviewed. Initial estimates indicate dog and cat population of approximately 250,000 and 200,000, respectively, in the two counties. A little over 40% of all households own either a dog or a cat or both. The human

population of the area is approximately 1,500,000.

No evidence for transmission of feline oncogenic agents to man or dogs was found, and data collected on 221 feline malignant lymphoma cases and matched control cats did not support the concept that horizontal transmission of infectious FeLV from cat to cat is an important mode of transmission. However, this would not exclude (a) occasional horizontal transmission and (b) transmission of infectious cat lymphoma virus in cats genetically resistant to lymphomatous or cancerous manifestations.

Significance to Biomedical Research and the Program of the Institute: The Animal Neoplasm Registry (ANR) of the California State Department of Public Health has been functioning since July, 1963. All cases are histopathologically confirmed and information is kept about the animal and the owner. This epidemiological study is important for determining the possible effects of exposure to cat leukemia and sarcoma viruses on human cancer and the importance of horizontal spread of virus from cat to cat and from cat to dog in maintaining the natural history of the feline viruses.

Proposed Course: The epidemiological survey will continue to completion.

Date Contract Initiated: June 19, 1969

Current Contract Level: $35,000

CALIFORNIA SCHOOL OF MEDICINE, UNIVERSITY OF (NIH-NCI-E-71-2147)

Title: RNA Directed DNA Polymerase and the Replication of Rous Sarcoma Virus

Contractor's Project Directors: Dr. J. Michael Bishop
Dr. Warren Levinson
Dr. Leon Levintow

Project Officer (NCI): Dr. Bernard Talbot

Objectives: Conduct investigations on the molecular biology of the avian and other RNA tumor viruses, particularly (a) the virion-associated DNA polymerase and (b) the virus-specific DNA and RNA in normal and transformed cells.

Major Findings: (1) Purified preparations of Rous sarcoma virus have been found to contain small amounts of double-stranded DNA; this DNA cannot be hybridized to viral RNA, but will reanneal completely with the DNA of avian cells. It thus appears to be derived from the DNA of the avian host

cell and is probably devoid of any function in the life cycle of the virus.

(2) Improved assays for virus-specific DNA and RNA in normal and infected cells have been developed. Both assays utilize the exceptional senstivity and specificity of single strand-specific nucleases from Neurospora crassa and Aspergillus oryzae. (a) The amount of virus-specific DNA present in cells is independent of the presence or absence of viral gs antigen, independent of infection with and transformation by oncornavirus, and independent of autosomal dominant traits determining a high incidence of virus-associated mammary carcinoma. For example, there was no genotypic difference detectable in the amount of MTV-specific DNA between the GR (high incidence of MTV and mammary cancer) strain and the C57BL/6 (low incidence) strain. This suggests that the inherited difference between the two strains resides in regulatory genes which govern the expression of viral information. Also, there were a similar number of multiple DNA copies of avian tumor virus genes found in normal or transformed chicken cells. These results suggest that all chicken cells contain a considerable amount of avian tumor virus genetic information and that the information may then be expressed in response to various factors such as inheritance of regulatory genes or stimulation by physical, chemical, or biological agents. (b) Virus-specific RNA has been detected in the nucleus and cytoplasm of infected cells, and the size of this RNA has been determined. Virus-specific messenger RNA has been isolated. A surprising finding is the presence of MTV specific RNA in the normal lactating breast of the C57 (low incidence) mouse. It is now feasible to perform detailed studies on the kinetics, chronology and mechanism of replication of viral RNA.

(3) The reverse transcriptase of Rous sarcoma virus has been purified 1,000-fold (2-4 molecules/virion) and found to consist of a maximum of two polypeptides with molecular weights 105,000 and 68,000. The purified enzyme closely resembles the polymerase activity of detergent-disrupted virions in both template response and nature of the DNA synthesized. The product DNA is small, and much of it is preferentially transcribed from a limited portion of the viral genome.

(4) DNA synthesis by the enzyme with 70S RNA as template is initiated on the 3' terminus of a polyribonucleotide. This primer molecule has been isolated and provisionally identified as 4S RNA known to be hydrogen-bonded to 70S RNA. Among the DNA polymerases tested, only oncornavirus reverse transcriptase is capable of extensively transcribing natural RNA templates in the absence of exogenous primer.

Significance to Biomedical Research and the Program of the Institute: These studies are providing an important insight into the mechanism by which RNA tumor viruses bring about malignant transformation, and perhaps will lead to significant advances in the understanding of the causation and control of human neoplastic disease. The contractor has made the important finding of no detectable difference in the amount of MTV-specific DNA between the GR (high incidence of MTV and breast cancer) and C57BL/6 (low incidence) strains of mice, as well as no detectable difference in the amount of avian tumor virus specific DNA in normal or transformed chicken cells. This suggests that all cells may contain tumor viral information (viral oncogene hypothesis) and that cancer is caused by the "switch-on" of the ubiquitously present oncogene.

Proposed Course: The polymerase of RSV will be purified to absolute homogeneity and its precise polypeptide constitution determined. The sequence of the RNA primer molecule associated with 70S RNA will be studied in sufficient detail to permit definitive identification. Various oncornavirus RNA's will be used as template for RSV polymerase and examined for preferential transcription of limited, homologous regions. The transcription of heterologous natural RNA's (e.g., poliovirus) will be studied with respect to extent of transcription, size and secondary structure of the transcripts and mechanism of initiation. The mechanism(s) by which isatin B-thiosemicarbazone inactivates both the reverse transcriptase and the infectivity of RSV will be examined in an effort to further implicate the enzyme in the biological activity of the virus. Transcription of natural RNA's (RSV, polio) by various cellular DNA polymerases will be studied with respect to primer requirement, extent of transcription and size and secondary structure of the transcript, all in an effort to accumulate further evidence that viral reverse transcriptase is unique among all known DNA polymerases. The assay of virus-specific DNA in normal and infected cells will be extended by means of a new technique to include sequences representative of the entire viral genome. Further evidence for covalent integration of viral DNA into host chromosome will be sought. The mechanism by which the expression of viral genetic information is controlled (repressed, partially or completely) in normal cells will be studied, principally by examining the relative extent to which viral DNA is transcribed in various normal cells, and by seeking factors which might influence that transcription.

Date Contract Initiated: June 2, 1971

Current Contract Level: $77,500

SCRIPPS CLINIC AND RESEARCH FOUNDATION (NIH-NCI-E-72-3264)

Title: Immunologic Study of RNA Tumor (Type C) Viruses

Contractor's Project Directors: Dr. Frank J. Dixon
Dr. Ralph A. Reisfeld
Dr. Richard A. Lerner

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: Part 1 - Dr. Frank Dixon: To develop and perform quantitative, highly specific, automated radioimmune assays for detection of ng amounts of gs and envelope antigens of the Type C viruses of mouse, cat, man, and others as specified, and for antibodies to these antigens.

Part 2 - Dr. Ralph Reisfeld: To obtain soluble coat antigens of mammalian Type C viruses in highly purified form and in sufficient amounts to produce highly specific antibodies against them.

Part 3 - Dr. Richard Lerner: To study the morphologic and quantitative aspects of cytoplasmic DNA synthesis after infection with RNA tumor viruses.

Major Findings: This is a new contract and major findings have not been reported.

Significance to Biomedical Research and the Program of the Institute: The etiological association between Type C viruses and cancer has been firmly established in a number of species, including chickens, mice, hamsters, rats, and cats. All three portions of this project deal with Type C viruses. Dr. Dixon's and Dr. Reisfeld's parts are involved in developing reagents which can be used for large scale screening to help confirm whether candidate human Type C viruses are, indeed, human and to document the incidence of these candidate human viral antigens and antibodies in human cancer patients. This is an essential part of the SVCP aim of determining the role of viruses in natural human cancer. Dr. Lerner's part of the proposal is important in understanding the mechanism of replication and transformation by RNA tumor viruses, with the ultimate objective of reversing the oncogenic process at the cellular level.

Proposed Course: (see Objectives)

Date Contract Initiated: June 20, 1972

Current Contract Level: $244,603

CALIFORNIA, UNIVERSITY OF (NIH-NCI-E-70-2048)

Title: Comparative Leukemia and Sarcoma Viral Studies

Contractor's Project Director: Dr. Leo K. Bustad

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: To further study the two simian Type C viruses (woolly monkey sarcoma and gibbon lymphosarcoma) which were first isolated in this laboratory.

Major Findings: (1) Woolly Monkey Fibrosarcoma (SSV): (a) SSV-infected bonnet monkey cells, cultivated in roller bottles, are yielding significant amounts of SSV virus. Several other cell lines of human, bovine, and simian origin also support SSV replication. (b) Bovine cells infected with woolly monkey sarcoma virus were inoculated into the autochthonous host at 10- to 14-day intervals as viable and freeze-thawed disrupted cells. Serum samples taken prior to inoculation and 6 weeks later were tested for antibody against the woolly monkey sarcoma virus by immunodiffusion. A positive precipitin band developed with a serum sample taken 6 weeks post-inoculation. (c) Radioimmune precipitation assays using SSV replicated in bovine thymus cultures were positive for bovine anti-SSV antisera but negative for bovine anti-FeSV antisera, indicating that SSV-infected cultures are free of FeSV antigens and that SSV and FeSV do not possess common envelope antigens. (d) Cellular and cell-free materials from tissue culture were inoculated subcutaneously into two newborn cotton-topped marmosets. Nodules (7 to 13 mm diameter) developed at the site of inoculation within 12 to 14 days. However, nodules regressed within 3 weeks. One nodule detected 28 days after inoculation reached 1 cm in diameter and has remained that size for 4 months. Blood samples from each animal have been examined monthly and no significant abnormalities have been noted. All inoculated monkeys are being held for continued observation.

(2) Gibbon Lymphosarcoma (SLV): (a) The cell line initiated from the gibbon tumor tissue remains the best producer of SLV, although bovine, African green monkey kidney (AGMK),

and human cell lines support low levels of SLV replication. (b) Transmission of the gibbon lymphosarcoma was tested in neonatal squirrel monkeys and pigs. Three of four newborn squirrel monkeys inoculated with gibbon lymphosarcoma tissue culture cells had a transient enlargement of the regional lymph node draining the site of inoculation. No signs of neoplasia have been observed during the 4 to 5 months following challenge; regular examination of blood samples has revealed no abnormalities. All monkeys remain under observation. Three of eight inoculated pigs were sacrificed 4 months after injection and found to have slightly enlarged mesenteric lymph nodes; histopathologic diagnosis was lymphoid hyperplasia. No other lesions were detected. Surviving pigs have shown no signs of neoplasia in the 7 to 9 months since inoculation and remain under observation.

Significance to Biomedical Research and the Program of the Institute: The finding at this laboratory of two Type C viruses associated with tumors of different primate species is evidence that the higher animals, including man, are likely to be among the growing number of species harboring oncornaviruses. Since monkeys and man are closely related phylogenetically, the proposed studies, which are oriented toward characterization of the primate viruses and seeking possible relation with human tumors, are of direct relevance in establishing the etiology of human cancer.

Proposed Course: (1) Characterize in greater detail the molecular components of the woolly monkey fibrosarcoma and gibbon lymphosarcoma viruses by analysis of enzymes, structural proteins and nucleic acid. (2) Determine the *in vitro* and *in vivo* biological activities of woolly monkey and gibbon lymphosarcoma viruses. (3) Initiate serologic studies for the detection of antigenic components in spontaneous tumors of simian and human origin that may be common to know simian RNA Type-C viruses. (4) Continue efforts to isolate oncogenic agents from spontaneous tumors of primates and complete limited studies on canine systems. (5) Complete studies on humoral antibody response in cats to the leukemia-sarcoma virus complex.

Date Contract Initiated: November 16, 1969

Current Contract Level: $550,000

EINSTEIN MEDICAL COLLEGE (PH43-NIH-NCI-E-65-612)

Title: Genetic and Immunological Factors in Viral Leukemogenesis

Contractor's Project Director: Dr. Frank Lilly

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: To gain a better understanding of the known or suspected genetic factors that play roles in the cancerous process.

Major Findings: (1) Studies of two inbred backcross systems show that within linkage group II of the mouse, the gene order is: theta - tk - d - Mod-1 - Fv-2, where these five loci code for, respectively, an antigen on thymic lymphocytes, tail kink anomaly, dilute coat color, an enzyme in the malic acid metabolism series, and susceptibility to Friend (and Rauscher) viruses. (2) AKR mice show a high incidence of spontaneous leukemia at around 8-11 months of age, whereas DBA/2 and (AKR x DBA/2) F_1 mice show no leukemia at this age; however, when these mice received methylcholanthrene paintings at 3 months, then (a) the leukemia in AKR mice occurred significantly earlier and (b) both DBA/2 and F_1 mice showed a marked incidence of leukemia, but this occurred at a rate still slower than unpainted AKRs. The results indicate that spontaneous leukemia in the AKR strain is recessive in this cross. However, the DBA/2 susceptibility to carcinogen-induced leukemia (and their resistance to carcinogen-induced skin tumors) is dominant in this same cross. (3) BALB/c and DBA/2 mice were previously not known to differ in their response to infection with F-B mouse leukemia virus; it is now found that 1-2 days after injection, copious virus bands (in sucrose gradients) appear in the sera of BALB/c mice, while there was little such virus in the sera of identically treated DBA/2 mice. C3H mice resemble BALB/c's in this respect, and D2.R^S mice resemble DBA/2 mice, which shows that the Fv-1 locus is not the determinant of this phenomenon. (4) This laboratory had previously reported that transplantation antigen H-2.31 disappears almost completely from spleen cells of BALB/c mice in the late stages of the Friend virus disease. It is now noted that there appears to be a gene present in some strains of mice which represses the expression of this antigen on erythrocytes (but which has no effect on the same antigen on lymphocytes) of mice known to have the H-2.31 antigenic determinant. (5) In studies on the genetic factors involved in the immune response to the H-2.2 histocompatibility antigen, it appears that two genes are involved in this

trait: one linked to H-2 itself (this gene is present in A mice) and the other at a locus independent of H-2 (this gene is present in BALB/c mice).

Significance to Biomedical Research and the Program of the Institute: One of the basic facts about tumor biology is that genetic mechanisms of the host exert strong control over the expression of oncogenicity. Dr. Lilly's work represents one of the few indepth studies being done on the genetics of susceptibility to viral oncogenesis. The knowledge derived from this study and the mouse strains developed will have broad applications both to the SVCP Program and the general effort in virus-cancer problems.

Proposed Course: Studies of: (1) The mechanism of the H-2 (histocompatibility genes) effects on leukemogenesis. (2) The mechanism of the Fv-1 and Fv-2 (susceptibility to Friend virus genes) effects on leukemogenesis (including determining if Rgv-2 is the same as Fv-1). (3) Map Fv-1, is Fv-2 related to H-7 (histocompatibility gene)? (4) Abelson lymphosarcoma virus (looking for the strain distribution of response, and if the virus consists of a helper plus a defective pathogenic component). (5) Friend virus radio-labeled (in vivo), to examine the component parts of the virus and its alternate forms of helper virus (N-, B-, or NB-tropic). (6) Immune response gene(s) for H-2.2.

Date Contract Initiated: May 13, 1965

Current Contract Level: $180,000

FLOW LABORATORIES, INC. (NIH-NCI-E-71-2097)

Title: Studies of Type C Viruses and Herpesviruses in Relation to Oncogenic Potential

Contractor's Project Director: Dr. Raymond V. Gilden

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: To conduct immunological and serological studies of oncogenic Type C RNA viruses and the herpes-like viruses associated with neoplasia. Virus proteins and RNA are purified in quantity, their structure analyzed, and the major protein used to prepare mono-specific antisera for immunological studies.

Major Findings: (1) Type C Viruses: (a) The major internal virion antigen (gs-1) of the RD 114 virus (candidate human Type C virus) has been purified by isoelectric focusing. The isoelectric point is 9.1, thus clearly distinguishable from the homologous protein of other mammalian Type C viruses; e.g., cat, 8.3; mouse, 6.7; hamster, 6.9; rat, 8.6. The purified protein was used to immunize guinea pigs and the serum showed a high degree of specificity for RD 114 in both complement-fixation and gel diffusion assays. Highly sensitive radioimmunoassay inhibition tests further indicated the lack of cross-reaction between RD 114 and FeLV, and also indicated qualitative differences between the gs-3 determinant of RD 114 and the non-primate Type C viruses. Gel diffusion tests with a polyvalent goat anti-FeLV serum (courtesy of Dr. Roger Wilsnack) also revealed two other FeLV specific proteins in FeLV which were not found in RD 114. (b) Successful rescue of the MSV genome from non-producer hamster tumor cells was accomplished by a cell fusion technique using Sendai virus. The rescued virus produced clear foci of transformed cells selectively on one of six human cell strains tested. (c) The gibbon and woolly monkey Type C viruses were found to possess the gs-3 determinants in gel diffusion tests (in collaboration with Dr. T. Kawakami); thus, this continues to be a distinctive feature of all mammalian viruses of this family. These viruses did not react with the species-specific antisera for cat, hamster, mouse, and rat viruses. The gibbon virus was also used to rescue the MSV genome from non-producer hamster tumor cells. (d) Attempts to demonstrate antibodies in 20 normal and tumored cats to the major internal protein of FeLV using radioimmunoassay procedures were unequivocally negative. This procedure gives at least 100-fold higher titers with control positive serum from immunized quinea pigs than complement-fixation tests. This test supports the earlier CF results indicating that animals are immunologically tolerant to their species-specific gs antigen. (e) Uridine is the 3' hydroxl terminal of the 70S RNA of all known Type C viruses. An estimate of the molecular weight of viral RNA based on terminal tritiation is ~2.5×10^6, consistent with a four subunit structure. (f) Antibody to the reverse transcriptase was obtained from rats bearing an AKR virus induced lymphosarcoma. This serum specifically inhibited mammalian Type C enzyme but not snake, chicken, or normal cell polymerases. A serum with a high degree of specificity for inhibition of the DNA dependent polymerase activity was obtained by immunization with purified feline virus enzyme. This serum exhibited the same species specificity as the tumored rat serum. (g) This contract has demonstrated and produced purified gs antigens from 10 different animal tumor viruses. These have been made available and used for extensive natural history studies of Type C RNA tumor viruses in mice, hamsters, rats, and

cats. Additional similar reagents are being produced for the candidate human RD 114 virus, the woolly monkey, and the gibbon ape virus.

(2) Herpesviruses: (a) Definitive evidence was provided for the persistence of EB virus in repressed state in virus "negative" lymphoblastoid cells. Virus was induced from the negative Raji cell by first making the cells resistant to BrdU and then removing the drug. Following drug removal, virus specific antigens and eventually complete virion appear in ~1% of cells. The carrier line P3HR-1, which produces viral antigens but not particles when grown in BrdU. After removal of BrdU, a low percentage of cells are able to incorporate thymidine and combined immunofluorescent and audioradiographic studies showed that it is these cells that synthesize viral antigens. The drug resistant cell lines offer a unique opportunity to study the mechanism of virus derepression since only thymidine kinase (TK) positive cells produce virus; thus, the high background of normal cell DNA synthesis (99% of the cells) is effectively screened out using thymidine or its analogues to study the nature of the DNA made after drug removal. (b) The immunoferritin technique has been used for differentiating antigens associated with Herpes simplex virions and for following the course of virus antigen production in situ. Using the immunoferritin technique, the specificity of heterophile positive infectious mononucleosis sera for EB virus was localized in the γM fraction, in contrast to "normal" human sera where anti-EB virus activity is localized in the γG fraction. This supports an etiologic role for EB virus or a serologically related virus in infectious mononucleosis.

Significance to Biomedical Research and the Program of the Institute: This project is deeply involved with the very important problem of determining whether viruses recovered from tumors are oncogenic in man. Since man will not be used as an experimental recipient, it is necessary to gain proof of oncogenicity by other means including seroepidemiological surveys for virus, virus antigen, and/or specific antibody. The contractor is producing and studying the virion antigens of Type C viruses and herpesviruses associated with neoplasia. Mono-specific antisera are being produced to these antigens, which are then used for seroepidemiologic studies carried out in a number of different laboratories; there is very active collaboration with the in-house VCB program, and with many other SVCP contractors (e.g., USC [PH43-NIH-NCI-E-68-1030], Microbiological Associates [NIH-NCI-E-70-2068], Univ. of Calif., Davis [NIH-NCI-E-70-2048], Princeton [NIH-NCI-E-71-2372], and Pfizer [NIH-NCI-E-70-2080]).

Proposed Course: (1) Large scale production of RD 114 virus and one other primate virus and preparation from them of

purified gs antigen, envelope antigens, and polymerase under rigid quality control. (2) Continued characterization of RD 114 virus including gs and envelope proteins. (3) Production of specific RD 114 gs antiserum and beginning of surveys of human materials for RD 114 gs antigen. (4) Continued production and characterization of other gs proteins by amino acid sequence analysis. (5) Purification of RD 114 virion RNA dependent DNA polymerase and production of specific antisera. (6) Search for specific non-virion proteins in infected and transformed cells. (7) Structure and terminal nucleotide sequence of viral RNA, and transformed cell virus-specific RNA. (8) Analysis of the sugar transport marker of sarcoma virus transformed cells. (9) Study of mechanism of EB virus derepression in lymphoblastoid cells. (10) Similar studies with fibroblasts in which Type C's can be evoked. (11) Investigations of herpes and Type C viruses using immunoferritin, immunofluorescence and enzyme labeled techniques, involving a subcontract with Dr. Konrad Hsu at Columbia University.

Date Contract Initiated: February 1, 1971

Current Contract Level: $2,410,000

THE JACKSON LABORATORY (PH43-NIH-NCI-E-67-744)

Title: Natural Occurrence of RNA Tumor Viruses (Genomes) and Host-Gene Control of Their Expressions

Contractor's Project Director: Dr. Hans Meier

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: The primary objective of this contract is to achieve an understanding of the mechanisms underlying the genetic determination of susceptibility and resistance to cancer and the RNA tumor viruses. There is little doubt that the expression of viral functions is in large part controlled by host genes. The Jackson Laboratory is a unique source of highly inbred mouse strains. These are used to define specific gene influences on Type C RNA virus/genome/tumor expressions under natural conditions, and the influence of environmental and other factors (carcinogens, aging) on host gene controls of oncogene and virus expressions.

Major Findings: (1) Host genetic rescue of murine leukemia virus: Complete infectious murine leukemia virus has been recovered by host genetic rescue in hybrids of two virus-free

lines of mice. Two autosomal dominant genes are required for the presence of complete virus. (2) Host-gene control of Type C RNA tumor virus: Genetic studies were aimed at elucidating the mechanism of inheritance of the group-specific antigen of the murine leukemia virus. Two approaches have been used. First, a classical Mendelian hybridization experiment was performed, utilizing mice of the high-leukemia AKR strain and the low-leukemia C57L strain, the first filial (F_1) generation hybrids, the second filial (F_2) generation hybrids, and the backcross generations of this cross. The second approach used a number of partially inbred lines derived from the F_2 generation of the same cross. The results of these studies demonstrated specific genetic regulation of expression of group-specific antigen. Genes ($Mlv\text{-}1^a$ and $Mlv\text{-}2^a$) permissive to the expression of the antigen are dominant or semi-dominant to their nonpermissive alleles ($Mlv\text{-}1^b$ and $Mlv\text{-}2^b$). (3) Chemical co-carcinogenesis: Experiments clearly indicate the host-gene control of both tumorigenesis and expression of function of endogenous Type C RNA tumor viruses. They lend support to the concept that cancer results from endogenous (host-genetic) or exogenous (acquired, carcinogen-induced) stimulation of an inherited viral genome. (4) Recombinant inbred (RI) lines, a new approach in genetic analysis: Two unrelated inbred strains are crossed and a number of inbred lines are developed from the F_2 generation by close inbreeding. The rationale for this procedure is that linked genes will tend to become fixed in the same combinations (parental) as they entered the cross. Unlinked genes are randomized in the F_2 generation and are therefore equally likely to be fixed in parental or recombinant phases. RI lines are particularly useful for analysis of (a) segregation, (b) linkage, (c) gene functions, and (d) mutations. Other advantages are (e) tissue from different individuals within an RI line may be pooled, without introducing genetic heterogenicity, (f) genetic differences tend to be maximized due to the elimination of heterozygotes, (g) the recessive characteristics of both parental strains are expressed in RI lines, (h) once RI lines are established, the time delay required for production of the segregating generations can be avoided, (i) genetic associations, due to either pleiotropy or linkage, may be detected between traits expressed in utero and adult characteristics, male and female limited traits, and traits that require killing individuals at different stages or require different pretreatments, and (j) the F_1 hybrid of the parental lines will accept tissue or organ grafts from any of the RI lines. (5) Genetic relationship between aryl hydrocarbon hydroxylase inducibility and chemical carcinogenesis: Inbred strains of mice show differential inflammatory reactivity and susceptibility to tumor induction following the topical application of polycyclic hydrocarbons. Strains also differ in the extent to which aryl hydrocarbon hydroxylase activity

is induced by these compounds. Differential inflammatory response and hydroxylase inducibility are genetically controlled by alleles at the In and Ahh loci, respectively. Genetic analyses and strain surveys have established that the In and Ahh loci are identical and that skin ulceration in response to topical carcinogen requires that aryl hydrocarbon hydroxylase activity be inducible.

Significance to Biomedical Research and the Program of the Institute: This program has contributed much of the basic data concerning the genetic determinants of oncogenesis and the natural expressions of the endogenous Type C RNA virus. It has pointed up the overwhelming influence of genetic predisposition in the development of natural cancer and susceptibility to environmental carcinogens. Contractor has developed sophisticated systems for defining and locating the genes and loci involved in murine oncogenesis, and virus and antigen expression, and has rescued complete virus through gene complementation by hybridization of two virus-free mouse strains. Information derived from this research bears direct relevance to the human cancer problem; definition of the heritable nature of cancer is essential to eventual control or prevention of the disease. These well defined murine systems and tissue cultures derived from them provide valuable vehicles for assay of environmental carcinogens and experimental therapeutic measures.

Proposed Course: (1) Development, characterization, and uses of recombinant inbred lines. (2) Study of genetic control of endogenous murine leukemia virus. (3) Study of association of the viral group-specific antigen with tumor development. (4) Genetic analysis of a dominant gene inhibiting expression of the group-specific antigen. (5) Mapping of viral structural genes by use of defective sarcoma virus mutants: complementation classes. (6) Additional marker studies for mapping structural genes of viral components. (7) Induction of complete or partial virus synthesis by drugs. (8) Chemical co-carcinogenesis studies. (9) Marker studies (immunogenetic and biochemical). (10) Study of genetic control of embryonic and post-natal, normal and abnormal cell proliferation. (11) Study of the effect(s) of hormonal stimulation of RNA metabolism in dwarf mice, and (12) host genetic rescue of murine leukemia virus.

Date Contract Initiated: May 2, 1967

Current Contract Level: $382,000

MICROBIOLOGICAL ASSOCIATES, INC. (PH43-NIH-NCI-E-67-697)

Title: Research on Animal Tumor Viruses

Contractor's Project Director: Dr. Robert M. Nims

Project Officer (NCI): Dr. Gary Kelloff

Objectives: The contract involves a long-term, comprehensive study to determine the natural incidence of Type C RNA virus expression and of cancer in nine strains of inbred mice and one strain of rat. The effort includes life time surveillance of defined strains for spontaneous neoplasms; serological testing of normal and tumor materials for the presence of Type C viruses and antigens; characterization of viral isolates as leukemia and cancer inducing agents; and the administration of hormones and carcinogens to study their effects on tumor and virus expression.

In addition to the research described above, the contract constitutes an important service to the SVCP. For specimens submitted for testing by NCI supported scientists, the contractor provides services which include storage and inventory of biological specimens, bioassays of leukemia and related viruses in a number of species, tissue culture and serological assays; also an extensive histopathology laboratory and pathological diagnostic service.

Major Findings: (1) Type C viruses isolated from spontaneous neoplasms of the BALB/c colony under study have been characterized in the CoMuL, SPAT, and XC tests as mostly B-tropic; viruses isolated from normal mice are mostly N-tropic, or a mixture of N- and B-tropic. (2) Studies have delineated the natural history of the Type C genome. Experiments in these aging colonies are now being focused on the tumor-inducing effects in vivo of the wild mice type viruses recovered from spontaneous tumors as well as from tumors induced by radiation, chemicals, and IdU. Preliminary results show that when injected into newborns the wild type viruses produce leukemia within 12 to 15 months. (3) Long-term cell-free passages of spleen and tumor tissues from spontaneous neoplasms have a highly significant association between virus isolation (SPAT and CoMuL tests) and induction of reticuloendothelial system neoplasms. (4) Streptonigrin (SN) has proven a potent inhibitor of Type C RNA virus replication with 87% inhibition achieved after 48 hours treatment and 98% after 120 hours. (5) A focus-forming sarcoma virus was recently isolated from a spontaneous sarcoma. This isolate produced diffuse transformation on BALB/c embryo cells, low frequency transformation on NIH Swiss embryo cells, and localized MSV-like foci on Fischer rat cells; the supernatant from transformed

embryo cells produced tumors in newborn BALB/c mice within 3 weeks after inoculation. This virus is of particular interest since it represents only the second sarcoma virus isolated from the mouse (the first was the FBJ virus, derived from a murine osteosarcoma). (6) Transplantation of two Fischer rat spontaneous leukemias to ACl rat newborns was successful. (7) Studies with Dr. Frank Portugal (NCI) showed that certain MuLV infected tissue culture cell lines have a natural repressor for MuLV replication in vitro and sarcomagenesis by MSV in vivo. The repressor is not an interferon or interferon inducer. (8) Experiments to determine the effect of extradiol and ovariectomy on uterine gs antigen expression have not revealed any appreciable differences between normal and hormone-deprived groups and are being terminated. A second series of hormone studies designed to elucidate the effect of diethylstilbesterol administered to pregnant Snell mice on cancer in their offspring (modeled after recent reports in humans) is nearing completion. (9) One of the major service efforts provides histopathological backup to this and other contract research. As an example of the scope, 3,600 slides were processed in October, 1971; two-thirds of the specimens originated from this contract program, and the remainder from other SVCP contracts.

Significance to Biomedical Research and the Program of the Institute: The service aspects of this contract are in direct support of the SVCP. Services include reagent production, serological tests, and histopathology for several laboratories. The surveillance of a number of animal colonies for their lifespan provided many of the key insights into the natural history of the oncogene. These virus-defined colonies are now being studied to determine how various endogenous and exogenous factors influence the carcinogenic effects of chemicals, radiation, etc. They also provide an excellent resource for isolation of natural inhibitors, and studies of interferon and vaccine effects on natural tumors.

This contract contributed importantly in ruling out the likelihood of vertical spread of Type C viruses in mice and also has provided much of the large body of information implicating the Type C genome in normal embryogenesis.

Proposed Course: (1) Assessment of oncogenic potential and in vivo growth capabilities of plaque purified B- and N-tropic MLV viruses isolated from normal and neoplastic cells. (2) Analysis of long-term neoplasia induction study involving the effect of age on tumor and virus induction by radiation or chemicals. (3) Attempt to produce high titered human interferon, study of interferon levels in germ-free and conventional mice, and study of interferon prophylaxis of spontaneous and chemically induced neoplasms. (4) Application

of specific immunofluorescent reagents to the study of the natural distribution of Type C RNA viruses in normal and neoplastic tissues. (5) Production of purified MLV envelope and gs antigens as immunogens for natural history and experimental studies. (6) With Dr. Frank Portugal (NCI), further characterization of effect of natural repressors and antibiotics on murine leukemia virus replication. (7) Determination of tumorigenicity of chemically transformed rat cell preparations in Fischer rats. (8) Continuation of providing services for other SVCP contracts.

Date Contract Initiated: November 15, 1961

Current Contract Level: $719,500

MICROBIOLOGICAL ASSOCIATES, INC. (NIH-NCI-E-70-2068)

Title: The Roles of Viruses and Chemicals in the Etiology of Cancer

Contractor's Project Director: Dr. Riley Housewright

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: Project A - Dr. Johng S. Rhim and Project B - Dr. Aaron E. Freeman: These projects are concerned with the development, evaluation, standardization and application of sensitive in vitro assay systems for studies of carcinogenic agents found in the environment to define the mechanisms of chemical and viral carcinogenesis in vitro, and to correlate these findings with in vivo studies of Projects C and D. Test systems include rat, mouse, hamster, and human tissue cultures at advanced levels of subculture, both uninfected and infected with various Type C RNA viruses. Materials under study include known and suspected carcinogens, derived from the natural environment (smog and tobacco smoke residues, food additives, hazardous industrial products) and provided by various collaborative contracting groups, particularly the program at USC (Contract PH43-NIH-NCI-E-68-1030), and large numbers of coded carcinogens and their analogs provided by Dr. John Weisburger (NCI).

Project C - Dr. Padman S. Sarma: This project is concerned with the development of sensitive in vitro assay systems for studying the prevalence of the naturally occurring feline, rat, avian, and other animal tumor viruses, utilizing the methodology previously developed under this contract. Dr. Sarma has been a primary contributor in designing test systems for rescue and detection of defective and endogenous tumor virus genomes utilizing trans-species rescue cell co-cultivation and sophisticated serological

techniques. These approaches are being intensively applied to various animal tumor systems having covert (switched-off) viral genomes in efforts to "turn on" overt expressions of the genomes, the ultimate objective being to apply successful methods to studies of human cancer.

Project D - Dr. Carrie E. Whitmire: This project tests RNA virus genome derepression by carcinogens in vivo, leading to gs antigen, infectious virus and/or tumor induction. The animal systems used include a variety of high and low leukemic incidence strains of mice, hamsters, and rats, including those strains from which tissue cultures were derived for Projects A and B. In addition to a variety of known laboratory carcinogens, suspected environmental carcinogens such as smog and tobacco products are included in test protocols concomitant with in vitro studies under Project B. Evaluation of carcinogenic effects is compared using different doses, routes of inoculation, age of animals, maternal parity influence, and other physiological and environmental factors which appear to be associated with susceptibility to tumor induction.

Project E - Dr. M. Lee Vernon: This project provides electron microscopy support to Projects A-D. The chief objective is to determine the prevalence of Type C RNA tumor virus particles in tumor tissues as well as normal embryonic and postnatal tissues taken at various ages.

Project F - Dr. John C. Parker: This project provides serological support to this and other VCB contracts.

Major Findings: Project A: Transformation was induced by extracts of city smog and tobacco smoke fractions in mouse embryo cells chronically infected with AKR leukemia virus, but uninfected mouse embryo cells were not transformed. The transformed cell lines produced tumors when transplanted into newborn homologous hosts.

A guinea pig embryo (GPE) cell line was found to be sensitive to chemical transformation. Also, GPE cells were transformed in vitro by Ki-MSV; the transformed cells contained both infectious virus and gs antigen.

Transformation of rat cells was achieved by the use of irradiated mouse cytomegalovirus (MCMV).

AKR virus infected NIH Swiss mouse embryo (ME) cells were readily transformed by chemical carcinogens (3MC, DMBA, and BP); this cell test system, when compared with rat and hamster systems proved to be the most sensitive test for carcinogenic chemicals.

Transformation by polyoma virus was facilitated by the use of established rat cell lines instead of primary or secondary cultures; transformation was further accelerated in rat cells chronically infected with RLV. The results suggest that the Type C RNA virus genomes provided not only oncogenic determinants for chemical in vitro transformation, but also for DNA virus cell transformation.

Polyoma transformed hamster embryo cells regularly led to hamster leukemia virus (HaLV) gs antigen after transplantation into newborn virus-free hamsters. Similarly, polyoma transformed NIH Swiss cells were shown to have Type C virus gs antigen when transformed cells were transplanted into virus-free NIH mice.

Project B: The synergistic activity of chemical carcinogenesis and Type C virus was studied in Fischer rat embryo cultures. Transformation appeared to be dependent upon a minimum level virus titer established in the rat cells at the time of chemical treatment. Cells treated with either agent alone or with chemical first, followed by viral infection after removal of chemical, remained normal.

The hamster Type C virus genome was shown to be ubiquitous in hamsters. In three hamster strains, tumors produced in vivo directly by inoculation of chemical carcinogens or by cells transformed in vitro by chemicals, polyoma virus or spontaneously, and tumor derived cell lines were frequently positive for Type C RNA virus by CF test.

Using a technique that separates cells according to their rate of attachment to glass, the reverse transcriptase activity of the candidate human Type C virus, RD 114, has been enhanced 30-fold. This virus has been adapted to grow in suspension cultures of a serial line of human prostate with a resultant four-fold increase in mature and immature Type C particles. Similar techniques have been successfully applied to the growth of woolly monkey and gibbon ape viruses in tissue cultures.

A series of chemical carcinogens and related inactive analogues have been tested for their ability to transform cells in vitro. In general, in vitro transforming activity was correlated with tumor production in vivo. However, a few "noncarcinogenic" agents did reveal transforming activity.

It has been shown that Type C oncogenic viruses were involved in chemically induced transformation in three separate systems: (a) Rat cells were not transformed by chemicals unless exogenous non-transforming MuLV was added. (b) Hamster cells were transformed by chemicals, but added HaLV decreased

the minimal transforming dose ten-fold. (c) Hamster cells transformed by chemicals produced tumors from which HaLV was regularly isolated.

Project C: RD 114 virus has the attributes of an infectious mammalian Type C virus and is unrelated to any of the various known avian and mammalian Type C RNA tumor viruses.

Endogenous latent Type C viruses of rats were activated in rat cell lines by treatment of cultures with 5-iododeoxyuridine and 5-bromodeoxyuridine.

The viral envelope antigens of feline Type C viruses responsible for viral infectivity were found to be responsible for induction of viral interference in the inoculated cultures against antigenically related challenge viruses. Three envelope antigens were detected which enabled classification of the feline Type C viruses into subgroups A, B, and C. The presently known members of the B and C subgroups, including three strains of feline sarcoma viruses, were found to be antigenic mixtures containing an A subgroup virus as one of the components. Virus purification of B and C subgroups was done by cloning techniques.

In rat cell lines releasing "defective" Type C particles, the viruses could not be rescued with defective murine sarcoma virus genomes. It appears likely that the cell lines, including three lines transformed by Rous sarcoma virus, contain the rat Type C virus in a "defective" state.

Prolonged passage of feline leukemia virus in human tumor cells (human rhabdomyosarcoma cells) did not alter the host range or envelope antigenic characteristics of the feline leukemia virus, suggestive of genetic recombination with a covert human Type C viral genome.

Project D: Studies of carcinogen induced tumors in various strains of inbred and random bred mice have provided a basis for strain selection and carcinogen dose to be used in future programs. While tumor incidence and latency is carcinogen dose dependent, there is considerable difference in the relative susceptibility of various strains. The incidence of gs antigen in the induced tumors is independent of the carcinogen or carcinogen dose used for tumor induction and reflects the natural gs antigen expression of the mouse strain; the tumors produced by carcinogens were "switched-on" in a high proportion of instances, while adjacent normal tissues remained "switched-off."

The phenomenon of mutual exclusion of leukemia and sarcoma neoplastic expression has been extensively studied in the AKR mouse strain. With sufficient doses of 3-methylcholanthrene

(3ME), subcutaneous tumors were produced which apparently prevented the expected spontaneous leukemias. Once the natural process of spontaneous leukemia induction had occurred, the resistance to subcutaneous sarcoma induction increased appreciably.

Studies with BALB/c and NIH Swiss mice of the effects of exogenous wild Type C RNA viral infection on 3MC induced sarcomas have shown the response to vary with the viral strain, the carcinogen dose, the mouse strain, the sequence of inoculation and the sex of the host.

Project E: In the last year almost 700 specimens were examined in the electron microscope for viral particles. A significant proportion of time has been devoted to studies of the RD 114 virus. Type C particles have now been observed in one or more hematopoietic tissues from embryos of 11 strains of mice while all strains were negative for Type C particles in muscle tissue at all gestational periods examined. Type B particles have been found in abundance in mammary tissues of wild mice 6 and 17 days in term, as well as in mammary tumors of the Claude substrain of BALB/c mice.

Project F: During the last year over 10,000 specimens were received on which over 20,000 serodiagnostic tests were performed. Many of the specimens were wild mouse sera received from USC (Contract PH43-NIH-NCI-E-68-1030) which were assayed for lymphocytic choriomeningitis and polyoma antibody, as well as for other naturally occurring mouse viruses.

Significance to Biomedical Research and the Program of the Institute: This contract represents a key part of SVCP's total effort. It has helped establish the role of the Type C viral genome in many feral and laboratory animal and cell systems. A number of test and assay systems developed under the contract are now used by laboratories throughout the world for investigating and characterizing RNA tumor viruses and their oncogenic and antigenic expressions.

Dr. Sarma's group has contributed no fewer than five highly sensitive serological (complement fixation, COFAL, COCAL, Neutralization, and interference) tests for field and laboratory use. Dr. Freeman's and Dr. Rhim's in vitro, rat, mouse, and hamster cell culture systems have provided new systems for sensitive and rapid assays of carcinogenic compounds in the natural environment. It is now possible to rapidly screen suspect compounds such as can be fractionated from smog and tobacco residues. The consistent correlations recently observed between in vitro transformation induced by the co-carcinogenic activity of RNA tumor viruses

and chemical carcinogens and in vivo tumor production by carcinogens have pointed up the feasibility of replacing current cumbersome, expensive and long-term in vivo bioassays with more efficient and sensitive in vitro systems. Dr. Whitmire's studies of the chemically induced expressions of the endogenous Type C viral genome are providing basic information on the effect of carcinogens in strains of mice having widely varied genetic susceptibilities to cancer. Dr. Vernon's EM studies have established a positive correlation of gs antigen content with the presence of Type C particles in various embryo organs. This correlation supports the concept of vertical transmission of the RNA genome. All these studies have furnished important evidence in support of the viral oncogene hypothesis.

There is extensive collaboration with numerous other groups supported by the SVCP; e.g., Microbiological Associates (PH43-NIH-NCI-E-67-697), USC (PH43-NIH-NCI-E-68-1030), California State Department of Public Health (PH43-NIH-NCI-E-68-997), and University of California (Naval Biomedical Research Laboratories [PH43-NIH-NCI-E-63-13]).

In summary, this contract is a core part of a coordinated comprehensive targeted research program to study the role of the Type C RNA virus genomes as determinants of ontogenesis and oncogenesis.

Proposed Course: Project A: (1) Currently available in vitro assay systems (particularly mouse cell) will be further used to screen the oncogenic potential of many additional environmental carcinogens. In addition, further efforts will be made to develop an in vitro assay system, utilizing human cell cultures. (2) KI-MSV transformed guinea pig embryo cells will be characterized. (3) Further studies on transformation of rat cells by exposure to irradiated cytomegalovirus are planned.

Project B: (1) Animal cell transformation systems developed in this laboratory will be used to identify and assay chemical carcinogens. (2) Efforts will continue using primate viruses to develop a human cell transformation system for identification and assay of chemical carcinogens. (3) Determination of the relationship between cell type transformed and histological type of tumor obtained by an in vitro transformation system utilizing "normal" epithelial cells. (4) Studies of transformation of virus infected cells cultured for many subcultures and comparison with spontaneous transformation in normal uninfected cells. (5) Utilization of labeled carcinogens to study the quantitative uptake, persistence and distribution of chemicals in cell culture.

Project C: Sensitive in vitro immunological and biochemical techniques are being developed for the quantitation of human and other primate candidate Type C viruses and antibodies to them.

Project D: In vivo studies will be begun on the effect of various viral inhibitors (interferon and active immunization with highly purified inactivated viral vaccines) on chemical carcinogenesis.

Other studies will include the relationship of genetic influences and natural viral genome expression on carcinogenesis in mice, rats, and hamsters. Studies will be undertaken to induce sarcomas in syngeneic mouse strains with viruses isolated from chemically induced sarcomas. The isolation of viruses from gs negative chemically induced tumors will be attempted using 5-iododeoxyuridine and 5-bromodeoxyuridine.

Project E: Electron microscopy will continue to search for the presence of Type C virus particles and other viruses and virus-like structure in normal and cancerous tissue and cultured cells.

Project F: Serodiagnostic laboratory support will continue to be provided.

Date Contract Initiated: February 1, 1970

Current Contract Level: $2,080,000

PRINCETON UNIVERSITY (NIH-NCI-E-71-2372)

Title: Studies on Surface Alterations in RNA Tumor Virus Transformed Cells

Contractor's Project Director: Dr. Max M. Burger

Project Officer (NCI): Dr. Gary Kelloff

Objectives: To study the surface alterations in transformed cells, as manifested by agglutinability with plant lectins.

Major Findings: Several RNA virus transformed tissue culture cell lines were investigated for increased agglutinability with plant lectins as was previously found by this contractor after transformation with DNA viruses. It was found that Rous virus (SR) transformed secondary chick embryo fibroblasts agglutinated slightly better than untransformed cells with jack bean agglutinin and that the increase was more pronounced with wheat germ agglutinin.

After treatment with purified hyaluronidase, cells agglutinated ten-fold better after transformation as compared with prior to transformation. That is essentially the same difference observed after transformation with DNA viruses.

When cells transformed with a temperature-sensitive Rous virus were shifted from the permissive to the nonpermissive temperature, they decreased their agglutinability and regained it only after shifting back to the permissive temperature. Decrease and increase in agglutinability were more pronounced if the cells were treated with hyaluronidase.

Some preliminary experiments have been carried out on Rauscher virus and Moloney sarcoma virus transformed mouse fibroblasts with Drs. C. Long and R. Gilden of Flow Laboratories (Contract No. NIH-NCI-E-71-2097). Increased agglutinabilities were found for both the producer and the non-producer lines as compared with the untransformed mouse parent cell lines. In this case, hyaluronidase seemed not to be necessary to observe sizeable differences in agglutinability.

Significance to Biomedical Research and the Program of the Institute: These studies aid in understanding the viral induced changes that occur in the molecular architecture of the cell surface upon transformation by RNA viruses. The surface changes of transformed cells are undoubtedly involved in the phenomena of unrestrained growth and metastasis of tumors.

Proposed Course: Continuation of work on mouse virus transformed mouse fibroblasts (together with Drs. C. Long and R. Gilden of Flow Laboratories), including examination of the effect of other agglutinins (in addition to wheat germ agglutinin) on these lines; the effects of trypsin and hyaluronidase and transformation by other RNA viruses will also be examined.

Date Contract Initiated: June 28, 1971

Current Contract Level: $56,898

SAINT LOUIS UNIVERSITY (PH43-NIH-NCI-E-67-692)

Title: Search for Viral-Specific Genetic Material in Human Cancers and Studies on the Mechanism of Oncogenesis by RNA and DNA Tumor Viruses

Contractor's Project Director: Dr. Maurice Green

Project Officer (NCI): Dr. Bernard Talbot

Objectives: This research program is aimed at understanding in detail the mechanism of cell transformation by RNA and DNA tumor viruses, applying new information on viral carcinogenesis and on the molecular biology of human cells directly to the problems of human cancer, and searching for inhibitors of polymerase that may control the expression of cancer specific genetic information.

Major Findings: (1) In order to analyze human cancers for virus genetic information, a variety of human cancer RNAs have been annealed with the DNA product of FeSV, FeLV (grown in human cells), MPMV (Mason Pfizer Monkey Virus grown in human or monkey cells) and MSV. The resulting hybrids were analyzed by hydroxylapatite chromatography and Cs_2SO_4 density gradient centrifugation. Carcinomas of the ovary contained RNA which hybridized with the MSV DNA product. Certain other human cancers contained RNA that hybridized with MPMV DNA and also with FeLV DNA (but not with FeSV or MSV DNA). These data may mean that sequences common to FeLV (grown in human rhabdomyosarcoma cells) and MPMV (grown in human or monkey cells) are present in human cancers.

(2) The 70S RNA genome of the murine sarcoma virus (MSV) and the avian myeloblastosis virus (AMV) contains adenylic-rich sequences (91% adenylic acid) of estimated molecular weight 0,000 to 60,000 (100 to 200 nucleotides) covalently linked to large viral RNA subunits. (A similar finding for Rous sarcoma virus and Rauscher mouse leukemia virus was reported by Lai and Duesberg).

(3) Inhibitors of polymerase molecules which may be used to control the expression of cancer-specific genetic information have been investigated. Of 37 rifamycin SV derivatives with 3-amine substituents, 29 were good inhibitors of the RNA→DNA polymerase activity of RNA tumor viruses, but they also inhibited host cell DNA polymerases. The most potent inhibitors, 3-piperidine derivatives with cyclohexyl or cyclohexylalkyl substituents show an activity of 4 to 5-fold greater than the analogous compounds with benzyl or phenyl substituents. A correlation was found between that ability of 3-cyclic amine rifamycin SV derivatives to inhibit DNA polymerase of RNA tumor viruses and of mammalian cells and to inhibit cell transformation. Of 182 rifamycin SV derivatives with 3-iminomethyl, 3-formyl hydrazone, 3-formyl oxime, 4-desoxy 3, 4-substitutions and 4-desoxy 4-substitutions and rifamycin B derivatives with 4-substitutions, 17 were moderately inhibitory at 20 µg/ml and 10 were strongly inhibitory derivatives. Several derivatives were effective at levels that may be useful for

clinical studies.

(4) At least two size classes of single-stranded RNA molecules sedimenting at 35S and 20S have been isolated from MSV transformed virus-producing mouse and rat cells. These viral RNA species are present both in free and membrane-bound polyribosome fractions of transformed cells. The cryptic state of MSV transformed non virus-producing hamster cells (HT-1) is characterized by two defects: a level of RNA only 2-5% of that present in virus-producing cells and a specific deficiency in 20S RNA. (5) Cells transformed by and continuously producing both sarcoma and leukemia viruses, but not those producing only leukemia viruses, are agglutinated by concanavalin A. It thus appears that the surface changes associated with agglutination are not necessarily associated with the malignant or transformed state of the cell, but may be a function of the expression of certain viral genes associated with sarcoma but not leukemia viruses. (6) Virus-specific RNA transcripts in cells transformed by adenovirus 2 and 7 contain cellular RNA sequences derived from highly reiterated cellular DNA sequences.

Significance to Biomedical Research and the Program of the Institute: Of the five areas listed below, under Proposed Course, the first is important in establishing the relationship of RNA tumor viruses to human cancer; the second is important because of the possible clinical use of these drugs to control the expression of cancer-specific information; the third and fourth are important since they may elucidate the transcription and translation of viral oncogenic information; and the fifth is important to understanding the regulation of macromolecular synthesis in normal and transformed mammalian cells.

Proposed Course: (1) A major effort is well under way on the molecular hybridization of the RNA from a large number of human cancers of defined organ types with DNA products of a variety of RNA tumor viruses, especially those of human and primate origin. (2) The search for and analysis of anti-polymerase drugs will be continued. (3) Analyses of the sequences of virus-specific RNA in non virus-producing transformed cells are continuing. (4) Attempts to isolate the cell-transforming proteins from transformed cells are planned; if demonstrated, their properties and functions will be studied. (5) Basic studies on the mechanism of growth control in normal virus-infected and transformed cells will be performed.

Date Contract Initiated: March 20, 1967

Current Contract Level: $1,200,000

SALK INSTITUTE (PH43-NIH-NCI-E-67-1147)

Title: Temperature-Sensitive Mutants of Polyoma Virus

Contractor's Project Director: Dr. Walter Eckhart

Project Officer (NCI): Dr. Stuart Aaronson

Objectives: To conduct studies on temperature-sensitive mutants of polyoma virus that are defective in functions required for cell transformation.

Major Findings: Temperature-sensitive mutants of polyoma virus have been isolated and characterized in order to identify the viral functions required for cell transformation. The mutants isolated so far can be placed into four or five functional groups, two of which are involved in cell transformation.

The ts3 gene product is required for induction of cellular DNA synthesis, viral DNA synthesis, and for cell surface alteration monitored by agglutination by wheat germ agglutinin or Concanavalin A. It is required for the maintenance of surface properties of transformed cells, and for loss of contact inhibition of DNA synthesis. The ts3 mutant does not complement other ts mutants. This could be explained if ts3 were defective in some aspect of uncoating or early gene expression at high temperature, or if ts3 were defective in a cis-active viral gene function. Temperature shift experiments in the presence and absence of cyclohexamide indicate that the ts3 function is expressed quite early after infection, and once expressed, is not required for the continuation of viral DNA synthesis. The mutant is not blocked; however, at some very early stage of adsorption or penetration, a conclusion that is supported by the observation that ts3 "eclipses" to the same extent, and with the same kinetics, as wild type polyoma during infection at permissive or nonpermissive temperature. It appears that the ts3 gene product is a regulatory protein (which may be part of the virion) whose function is required for the expression of several virus mediated functions during lytic infection, and in the transformed cells.

The gene product of the ts-a mutant is required for viral DNA synthesis and for stable transformation, but not for induction of cellular DNA synthesis or for abortive transformation.

The NG-18 mutant is a host range mutant that is unable to transform hamster or rat cells. NG-18 will genetically complement the "late" mutants that make viral DNA, but do not make infectious virus, at high temperature, and also

mutants in the ts-a group that are defective in transformation at high temperature.

Significance to Biomedical Research and the Program of the Institute: The development of systems of temperature-sensitive mutants of oncogenic viruses represents the application to cancer research of a powerful tool of modern biology. Using the temperature-sensitive mutants, it should be possible to define which viral genes are responsible for the establishment and maintenance of transformation.

Proposed Course: Studies of temperature-sensitive mutants of polyoma virus will continue, as will studies of viral DNA synthesis in isolated cell nuclei, trying especially to promote more efficient initiation of DNA synthesis in the system. The process of infection by viral DNA and DNA-protein complexes will be studied.

Date Contract Initiated: June 5, 1967

Current Contract Level: $120,000

SOUTHERN CALIFORNIA SCHOOL OF MEDICINE, UNIVERSITY OF and CHILDREN'S HOSPITAL OF LOS ANGELES (PH43-NIH-NCI-E-68-1030)

Title: A Comprehensive Field and Laboratory Research Program on the Etiology and Epidemiology of Human Cancer

Contractor's Project Directors: Dr. Murray B. Gardner (USC)
Dr. Robert M. McAllister
(Children's Hospital)

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: To mount a multifaceted, highly interrelated program designed to determine the roles of viruses, physical and chemical carcinogens, and other factors in the etiology of human and animal cancer in a natural urban ecology. These studies are carried out at USC School of Medicine and at Children's Hospital of Los Angeles.

Viral studies: Human, pet, and feral animal cancer and fetal materials are under intensive study for RNA tumor virus expression, utilizing all the modern in vitro, as well as in vivo, test systems. Extensive field studies and procurement efforts provide large numbers of tissues derived from cancer patients, genetically defective individuals, and spontaneous and therapeutic abortions. These materials are utilized for in vitro and in vivo biological studies and are subjected to serological, immunological, biochemical, and electron micrographic analyses designed to detect, isolate,

and characterize the RNA viruses and virus-specific antigens associated with naturally occurring animal and human neoplasms.

Epidemiological studies: This program is providing, through hospital record surveys and community questionnaire surveys, up-to-date information of the natural occurrence of human cancer, as it may be influenced by genetic, viral, environmental, or other factors, including exposure to variable smog components in differing ecological areas of Los Angeles County, industrial and household carcinogens, and pets with and without cancer. Other factors such as occupation, aging, genetic defects, smoking, hormone therapy, and immunosuppressants are being studied using classical epidemiological methods combined with virological and serological surveillance.

Environmental studies: This program is concerned with monitoring focal environmental areas for levels of carcinogens and other air pollutants. Materials collected are characterized and supplied to laboratories at USC, as well as to NCI and other SVCP contract programs; e.g., Contract No. NIH-NCI-E-70-2068, for studies to determine the carcinogenic activities of such pollutants in tissue culture and in animals.

Co-carcinogenesis studies: This area is concerned with testing the carcinogenic effects of selected chemical and environmental carcinogens in various inbred and feral strains of mice, hamsters, and cats in vivo, and in selected RNA-virus-infected mammalian tissue culture systems.

Major Findings: A candidate human Type C virus, RD 114, was rescued by Dr. Robert McAllister's group at the Children's Hospital of Los Angeles, working in collaboration with Dr Murray Gardner (USC) and Dr. Padman Sarma (NCI). Rescue was effected by transplantation of human rhabdomyosarcoma cells (RD cells) into a fetal kitten. The RD 114 virus isolated was, at first, assumed to be a feline leukemia virus, but was found not to contain the FeLV gs-1 or envelope antigens. Further tests in a number of collaborating laboratories have confirmed the RD 114 to be a Type C RNA virus possessing the mammalian group specific antigen (gs-3), but a unique gs-1 antigen.

RNA extracted from RD 114 consisted of 65-70S and 4S components and had reverse transcriptase activity which utilized endogenous 70S RNA or the synthetic polymer poly rA.dT as template.

Preliminary DNA-RNA hybridization experiments in collaboration with Dr. Marcel Baluda at UCLA suggest that the nucleotide

sequence of the 70S RNA of the RD 114 virus is different from the nucleotide sequences of the RNA from two strains of FeLV.

Characterization of the RD 114 virus is continuing in a number of laboratories, including the Viral Carcinogenesis Branch (NCI), Drs. Freeman and Rhim at Microbiolgical Associates (NIH-NCI-E-70-2068), Dr. Bishop at University of California (NIH-NCI-E-71-2147), Dr. Green at St. Louis University (PH43-NIH-NCI-E-67-692), Drs. Gilden, Oroszlan, and Hatanaka at Flow Laboratories (NIH-NCI-E-71-2097), Dr. Rabin at Bionetics (NIH-NCI-E-71-2025), and on site Drs. McAllister, Nicolson, Gardner, Roy-Burman, Rongey, and Rasheed.

RD cells were productively infected with GA-FeLV and in contrast to RD 114 virus, the virus released (RD-FeLV) did have FeLV specific envelope and gs-1 antigens.

RD cells productively infected with KiMSV contained murine virus gs-1 antigen (but not RD 114 gs-1 antigen) and the progeny virus, although not causing focus formation, has a tropism for human and rat cells but not mouse cells.

Biochemical studies of KiMSV and RD-FeLV were continued; in particular, characteristics of their reverse transcriptase reactions.

Transformation and productive infection of a human osteosarcoma cell line with GA-FSV was achieved.

DNA isolated from human adenovirus type 1 was found to be infective for human cells.

A highly efficient method for induction of latent Type C RNA viruses was discovered using BrdU. This method was applied to several human tumor cell lines or primary cultures from human malignancies. Under conditions which regularly led to detection of Type C RNA viruses in rodent or avian culture, no viruses were detected in human cells.

Host dependent antigenic modification of KiMSV was studied on the virus propagated in mouse and rat cells. Type specific antigenicity and in vitro host range (but not the group specific antigenicity) were found to be reversibly host dependent.

Nonproductive lines and monocellular clones transformed by KiMSV were derived from normal rat kidney (NRK) line. They were characterized for virus production by focus assay, COMUL test, electron microscopy, and H^3-uridine incorporation and found to be free of Type C viruses.

High molecular weight (70S) RNA isolated form KiMSV induced transformation in NRK cells. Transformed cells did not release detectable virus but did contain rescuable viral genome.

An inhibitor, very likely an antibody, directed against the DNA polymerase of the mammalian Type C RNA tumor viruses, was detected in the sera of cats with spontaneous tumors or FSV induced sarcomas.

Twenty-three nontransforming, mostly N-tropic, Type C isolates were recovered in vitro from wild mouse embryo cells, breast tissue, and 3-MC-induced sarcomas. Eighteen of these isolates were obtained from mice of one trapping area in which a very high prevalence (80-90%) of Type C virus activity was detectable. This colony is interesting and may reflect a peculiar segregation of genes of a very atypical nature since all of a dozen other normal wild mice populations were negative for this virus.

Two sarcoma viruses have been isolated in vitro, one of which has so far produced sarcomas in vivo in wild mice. Both sarcoma isolates were found to grow better at 32° (close to normal mouse body temperature), than 37°, a finding which may have potential importance in other tissue culture systems as well. Most virus-negative wild mouse cell cultures were resistant to infection with exogenous Type C virus of wild mouse origin.

Type B virus particles have been found by EM in over 50% of the breast biopsies from pregnant mice trapped throughout Los Angeles County; thus, wild mice provide a natural source of the difficult to obtain mammary tumor virus particles.

Of the dozen separate wild mouse colonies under study, one revealed a high level of infection with polyoma. In view of the cancer-inducing properties of polyoma in experimental systems, this colony is of particular interest to determine what effect, if any, polyoma has on cancer incidence, age at onset, effect of carcinogens, etc., in its natural host.

An excellent correlation between the detection of FeLV gs-1 antigen (using guinea pig sera prepared against this purified antigen by Dr. R. Gilden of Flow Laboratories, Contract No. NIH-NCI-E-71-2097) and Type C particles by EM has been obtained in cats with spontaneous lymphoma, unexplained severe anemia, and in normal cats. Cats with unexplained severe anemia had as much, or even more (80-90%), Type C virus expression than cats with spontaneous lymphoma. Virus particles and gs-1 antigen were detected in about 10% of normal cats. Cultures obtained from tissues of 7 of 26

different fetal cats contained demonstrable Type C virus activity in early subpassage.

Eighty-three hospitals, representing more than 70% of the 30,000 eligible acute hospital beds in Los Angeles County, are participating in the Cancer Surveillance Program. Approximately 10,000 current cancer cases have been collected, abstracted, recorded on computer tape, and are being analyzed. Field studies of several types of cancers occurring in populations at Leisure World and several other seroepidemiological studies are under way. Epidemiologic studies are in progress on (a) the possible role of the putative human Type B particle in the pathogenesis of human breast cancer; (b) Hodgkin's disease and EBV; (c) young genital tract cancer, particularly in relation to maternal stilbesterol; and (d) human lymphocyte antigen phenotypes in relation to human cancer.

Samples of air pollutants have been collected. Crude extracts and some subfractions have been provided to Drs. Freeman and Rhim at Microbiological Associates (Contract No. NIH-NCI-E-70-2068), Rasheed at USC (Contract No. PH43-NIH-NCI-E-68-1030), and Weiss at USC (Contract No. NIH-NCI-E-72-2032). Most of the fractions studied in vitro have been found to have some transforming activity. Samples of these extracts are available to other interested investigators.

Significance to Biomedical Research and the Program of the Institute: This program searches for causes of human, pet, and other animal cancers in a natural ecology, utilizing (1) experimental animal systems; (2) basic viral and chemical carcinogenesis studies; and (3) epidemiological profiles of cancer incidence in Los Angeles Area humans and animals in relation to exposure, and to environmental carcinogens.

In addition, the program continues as a prime resource for supplying human and animal materials to the Viral Oncology in-house and SVCP contract programs, particularly to Microbiological Associates (NIH-NCI-E-70-2068), Flow Labs., Inc. (NIH-NCI-E-71-2097), St. Louis University (PH43-NIH-NCI-E-67-692), University of California (Naval Biomedical Research Laboratories [PH43-NIH-NCI-E-63-13]), and the California State Department of Public Health (PH43-NIH-NCI-E-68-997).

Proposed Course: Continuation of (1) studies with the candidate human Type C virus, RD 114, (2) studies of mouse and cat Type C viruses, (3) co-carcinogenesis studies, (4) epidemiological studies of factors influencing cancer incidence, (5) characterization of air pollutants. (6) Procurement, growth, and distribution of human and animal materials.

Date Contract Initiated: June 26, 1968

Current Contract Level: $2,499,040

SOUTHERN CALIFORNIA SCHOOL OF MEDICINE, UNIVERSITY OF (NIH-NCI-E-72-2032)

Title: Conditional Lethal Mutants of RNA Tumor Viruses

Contractor's Project Director: Dr. Peter K. Vogt

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: (1) Conditional lethal mutants of avian sarcoma viruses will be isolated. (2) All mutants will be tested for leakiness and genetic stability. (3) The reproductive and cell transforming abilities of the mutants will be delineated under permissive and nonpermissive conditions. (4) The location of the conditionally lethal step in the infectious cycle will be determined. (5) The epidemic of chicken tumors occurring in Southern California in the Autumn of 1971 will be studied.

Major Findings: The contractor has been collaborating with Dr. Gardner's group (Contract No. PH43-NIH-NCI-E-68-1030) in studies of a major epidemic of tumors which occurred in chicken populations of Southern California during the Fall of 1971. The epidemic appeared to coincide with the delivery of the first batches of chickens which had received the new Marek's disease vaccine. In such chicken populations condemnations due to Marek's disease leukosis had declined; however, at the same time a rise in the incidence of solid tumors occurred. These tumors included sarcomas, Wilms tumors, and hemangiomas.

Fresh chicken tumor specimens were obtained and put in culture with normal chicken fibroblasts serving as feeder layers. In about half of the tumor cultures a cytopathic rounding of the feeder cells occurred and eventually spread through the entire culture causing cell death. The effect could be transferred to normal chicken and quail fibroblasts with cell-free supernatants of the infected cultures. However, freezing and thawing of these supernatants led to almost complete loss of activity. Low multiplicities of infection resulted in the formation of foci consisting of rounded cells not unlike those transformed by Rous sarcoma virus. However, these cells failed to pile up and lacked the capacity for prolonged growth. Infected cultures were studied by electron

microscopy in Dr. Gardner's group. Both herpesvirus and Type C particles were seen. Complement fixation tests of the tumors (carried out in Dr. R. Huebner's laboratory) indicated that the group specific antigen of avian RNA tumor viruses is present in the tumor tissue in greater concentration than in normal tissues.

The data available so far are compatible with the suggestion that the cytopathic effect seen in culture is caused by a herpesvirus. Whether this virus is also responsible for the tumor formation in vivo is not known at the moment. The spectrum of tumors seen in the chicken population (hemangiomas, sarcomas, and Wilms tumors) is more indicative of an avian RNA tumor virus than of Marek's disease herpesvirus. Experiments are in progress to inactivate the herpesvirus component in tissue culture samples selectively and to identify the surviving Type C particles. Infected cultures have also been frozen and are available to qualified investigators.

Significance to Biomedical Research and the Program of the Institute: RNA tumor viruses are oncogenic under natural conditions and probably occur in all vertebrates including man. It is therefore important to understand their mode of replication and the mechanism of their oncogenic action. A difficulty has been in differentiating between cellular and viral macromolecular synthesis. Conditional lethal mutants could alleviate this situation because accumulation of viral precursors will occur under nonpermissive conditions. The levels of viral material reached in the cell may thus become detectable with currently available biochemical techniques. Conditional lethal mutants will also be useful in delineating the sequence of viral functions during infection and in pointing out patterns of inter-dependence in such functions.

Even more important than the contribution temperature-sensitive mutants may make to our understanding of virus replication is their potential value for the analysis of neoplastic transformation. Inability of temperature-sensitive mutants to transform under nonpermissive conditions would strongly implicate the viral genome in the process of transformation. Transformation negative mutants which can transform at 35° but are unable to perpetuate transformation at 41° will be significant in the identification of specific viral products and functions which are needed for the maintenance of the neoplastic state. Preliminary observations with avian sarcoma viruses indicate that such types of mutants can be obtained.

Proposed Course: Since the work being currently done on the epidemic of chicken tumors is an interim project, it is

planned to conclude this work by characterizing the RNA tumor virus components obtained from the tumors; work will continue further with these agents only if they are able to produce transformation in vitro and can be used directly in mutant work.

It is anticipated that very shortly the equipment needed for the isolation and characterization of new temperature-sensitive mutants will be delivered, and the work on temperature-sensitive mutants will begin.

Most work will be carried out with avian sarcoma virus B77. Chick embryo fibroblast cultures infected with a high multiplicity of virus become completely transformed within a few days and actively produce virus. Such cells will be exposed to 5-azacytidine (1-25 µg per ml) which has been shown to cause mutations in replicating RNA viruses. Virus stocks grown in the presence of the mutagen for 24 hours will be harvested and studied for the presence of conditional lethal mutants.

As in previous work, incubation at 41°C will be chosen as nonpermissive condition, and 35°C will constitute the permissive environment. All temperature-sensitive mutants will be classified according to the viral product or function which is missing at the nonpermissive temperature. Products and functions which will be tested in this initial classification are (1) neoplastic transformation of the infected cell, (2) production of infectious or noninfectious viral particles, (3) synthesis of type-specific antigen, (4) synthesis of group-specific antigen.

The approximate location of the temperature-sensitive step in each conditional lethal mutant will be determined by shifting the temperature of incubation at various times after infection from 35-41° or vice versa. It will be possible to divide the mutants in two categories, one having an early temperature-sensitive step and the other showing late temperature sensitivity.

Date Contract Initiated: October 15, 1971

Current Contract Level: $256,000

STANFORD UNIVERSITY (NIH-NCI-E-69-2053)

Title: (A) Procurement, Processing, Storage, Distribution and Study of Human Tumor cell Cultures; and (B) Operation of a Central Mycoplasma Diagnostic Laboratory

Contractor's Project Director: Dr. Leonard Hayflick

Project Officer (NCI): Dr. Stuart Aaronson

Objectives: Part A is for the procurement, processing, and distribution to SVCP contractors of viable, characterized human tumor cell cultures obtained from biopsy or surgical removal at hospitals in the San Francisco Bay Area. (Serum samples are collected simultaneously.) In addition research studies are directed toward the detection of a viral genome in these cells. Part B serves as a central diagnostic facility for the detection and identification of mycoplasma contamination in virus preparations, sera, cell cultures, and clinical materials submitted by other SVCP contractors. Upon request, identification of isolates is made as to species; and mycoplasma antigens are distributed to those investigators requiring these materials.

Major Findings: (1) Over 68 human tumors were cultivated during the year. All viable cultures have been photographed, and from 3 to 11 ampules of tumors have been stored in liquid nitrogen. (2) All tumor culture data, patient history, and cell storage information is now stored in a computer. (3) Thirteen human tumor cell populations have been examined by electron microscopy for Type C particles with negative results. (4) With cytochalasin B, enucleation of the entire culture of human normal (WI-38) and cancer cells has been achieved, thus paving the way for hybridization and genome rescue experiments. (5) The use of antilymphocyte-serum (ALS) treated mice in assessing the malignancy of human tumor cells is continuing. ALS has now been prepared against the C57/L strain of mouse (one of the most "switched-off" strains in terms of Type C particles), in which future studies will be done. (6) Treatment of WI-38, human embryo cells, and human amnion with benzo-(a)-pyrene or methyl-cholanthrene or FeSV does not result in a malignant transformation. (7) During 1971, 3,156 samples were received from SVCP laboratories and were tested for mycoplasma contamination; 358 were positive. (This represents the largest number of mycoplasma samples received in any year since the inception of this contract 7 years ago.) (8) Studies continue on the growth characteristics of mycoplasmas in an effort to understand the interaction of mycoplasmas with cells cultured in vitro and the effects of new mycoplasma inhibitors with the goal of developing a control for mycoplasma contamination.

Significance to Biomedical Research and the Program of the Institute: The mycoplasma diagnostic facility is a testing and monitoring service available to all SVCP contractors and Viral Oncology intramural staff. Many of the most important viral specimens, cell cultures, sera, etc., used in the Viral Oncology Program are sent to this facility for mycoplasma testing. In addition the contractor is growing

human tumor cells in vitro as a resource for other SVCP contractors and for the purpose of his own research on transformation of cells by oncogenic viruses. The system of C57/L mice treated with anti-lymphocyte serum will be used to tell whether cells from neoplastic tissues, being grown in vitro, are "tumor cells or fibroblasts."

Proposed Course: (1) Continuation of collection, cultivation, characterization, and storage of human tumor cells, as well as mycoplasma testing of samples received from other laboratories. (2) Continuation of studies on: (a) effects of various chemical carcinogens on normal human cells in vitro, alone and in combination with oncornaviruses; (b) discrimination by C57/L mice treated with antilymphocytic sera (ALS) between human normal and cancer cells; (c) cell fusion, hybridization and keterokaryon formation in vitro using cytochalasin B and Sendai virus. (d) Detection of gs antigen in human embryonic tissue and tumor cells. (e) Electron microscopy of cultured human tumor cells. (f) Attempts to transform a variety of normal human cells with RNA tumor viruses.

Date Contract Initiated: June 19, 1969

Current Contract Level: $178,447

WASHINGTON, UNIVERSITY OF (NIH-NCI-E-71-2171)

Title: Studies on Tumor-specific Transplantation Antigens

Contractor's Project Directors: Dr. Karl Erik Hellström
Dr. Ingegerd Hellström

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To detect and characterize tumor-specific antigens, plus serum-mediated and cell-mediated immune responses to these tumor-specific antigens, in human tumors.

Major Findings: (1) Human neoplasms derived from the same tissue had been previously shown, by the contractor, to have common tissue type specific tumor associated antigens since lymphocytes from a given cancer patient will inhibit his own tumor cells in tissue culture and also tumor cells of other patients of the same histologic type, but not of different histologic types. Evidence was now found for the existence of analogous antigens common to both rat bladder papillomas and carcinomas, and for such antigens common to mouse bladder carcinomas. Murine bladder tumors may thus be suitable for an investigation of immune reactions against tumor associated antigens of the tissue specific type. Rats

immunized with syngeneic urinary bladder papillomas, then challenged by insertion of a methylcholanthrene pellet into the bladder, were found to develop fewer primary bladder tumors than rats immunized with normal bladder tissue.

(2) The contractor had previously shown that human tumors of the same histologic type have common blocking antibodies since the serum from a given patient will block the tumor-destructive effect of his own lymphocytes for his own tumor and also for tumors of the same histologic type from other patients. It was now shown that in addition to sera a similar blocking activity can be eluted at pH 3.1 from human tumor tissues, obtained at surgery (seminomas and osteogenic sarcomas), and from tumor cells growing in ascites and pleural effusions (carcinomas of endometrium, breast, and ovary). A high (MW above 100,000) and a low (MW below 100,000) molecular weight fraction can be separated from the eluates by ultrafiltration. Neither of these fractions could block lymphocyte mediated cytotoxicity in vitro when tested by itself, while a 1:1 mixture of them could. Blocking was also obtained when the tumor cells were first exposed to the high and then to the low molecular weight fractions, but not when the sequence was reversed. The observations obtained are analogous to previous findings in animal tumor systems and provide evidence that tumors growing in human patients are coated by "blocking factors."

(3) Blocking material, in the form of sera of rats carrying progressively growing polyoma tumors and low pH eluates of polyoma tumor tissue inoculated into polyoma isografted rats, cause an enhanced tumor growth.

(4) Sera from all of seven tumor patients tested (one with melanoma, one with colonic carcinoma and five with breast carcinoma), who had become clinically tumor-free, could "unblock" the blocking effect of sera from patients bearing tumors of the respective types, thus making it possible for immune lymphocytes to kill cultivated neoplastic cells in the combined presence of the "unblocking" and blocking sera.

(5) "Unblocking" antibodies can be produced by immunization of BCG primed rats or rabbits with tumor cells. These antibodies can counteract the effect of specific blocking sera and tumor eluate in vitro. When inoculated into rats which had previously received a polyoma tumor isograft, unblocking serum was found to inhibit the appearance of (or counteract) the blocking activity of serum in four of five rats. Tumors in these four rats grew progressively for 10-12 days and then completely regressed.

Significance to Biomedical Research and the Program of the Institute: This important and productive study of human and animal tumor antigens, as well as cell-mediated and humoral immune responses to the antigens, has already given, and promises to continue to give, insights to the understanding of the body's immune response to tumors, and ultimately may lead to immunotherapy of established tumors in man.

Proposed Course: Continuation of screening of human and animal tumors for tumor-specific transplantation antigens. Continuation of *in vitro* studies of cell-mediated and humoral immune responses against TSTA, including "blocking" and "unblocking" factors, and attempts at immunotherapy of established tumors.

Date Contract Initiated: April 14, 1969

Current Contract Level: $90,000

WEIZMANN INSTITUTE OF SCIENCE (NIH-NCI-E-69-2014)

Title: Study of Virus-induced Tumor-specific Transplantation Antigens

Contractor's Project Director: Dr. Leo Sachs

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To investigate the differences between the structure of the surface of normal cells and of cells transformed by viral and non-viral carcinogens by studying the differential binding of plant lectins.

Major Findings: Concanavalin A (Con. A) agglutinates transformed cells, but it only agglutinates normal cells after they have been treated with tyrpsin. Only about 15% of the cell surface is occupied by Con. A molecules at saturation.

Transformed cells were agglutinated by Con. A at 24°C but not at 4°C. Agglutination of transformed cells by wheatgerm agglutinin, which binds to N-acetyl-D-glucosamine-like sites, and by soybean agglutinin, which binds to N-acetyl-D-galacyosamine-like sites, was not temperature-sensitive.

Changes in the structure of the cell surface were found in the ascites form of a Moloney virus-induced lymphoma, and in cells transformed by polyoma virus, SV40, Rous sarcoma virus, and the chemical carcinogen, dimethylnitrosamine.

Cells of a Moloney virus-induced lymphoma (YAC) were agglutinated by Con. A, wheatgerm and soybean agglutinins. However, only Con. A showed a marked toxic effect on YAC cells in vitro and in vivo. In vitro incubation with 125 μg Con. A for 24 hours lysed 95% of the cells. Intraperitoneal injection of 1 mg Con. A at 1 hour, 2 days, and 5 days after intraperitoneal inoculation of 10^2 YAC cells into adult mice resulted in an inhibition of tumor formation in 70%, 50%, and 20% of the animals, respectively.

Amino acid and carbohydrate transport in normal and malignant transformed hamster cells was studied after equal binding Con. A to the cell surface. The transport of a number of amino acids was inhibited after Con. A binding in the transformed cells but not in the normal cells (e.g., L-leucine, L-arginine, L-glutamic acid, L-glutamine, cycloleucine, and α-aminoisobutyric acid). Transport of D-glucose and D-galactose was more inhibited by Con. A in transformed than in normal cells. There was no effect on the transport of L-fucose or 3-O-methyl-D-glucose in either normal or transformed cells.

Significance to Biomedical Research and the Program of the Institute: Compounds that interact differentially with the surface of normal and tumor cells are of value in elucidating the chemical nature of the differences in the surface that are associated with cell malignancy. They are also of potential value for tumor chemotherapy.

Proposed Course: The potential therapeutic value of Con. A will be further explored in three main directions: (1) Chemical modifications of Con. A to attempt to improve the degree of previously shown differential toxic effect on normal and tumor cells. (2) Studies of what enables Con. A to produce cell toxicity (how it differs from other lectins which bind but do not kill). (3) Further studies of the ability of Con. A to induce the activation of lymphocytes.

Date Contract Initiated: April 22, 1969

Current Contract Level: $51,600

WISTAR INSTITUTE OF ANATOMY AND BIOLOGY (NIH-NCI-E-71-2092)

Title: Extraction and Characterization of Virus-induced Transplantation Antigen and Rescue of Virus from Sarcomas and Leukemias

Contractor's Project Director: Dr. Anthony J. Girardi

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To extract and characterize tumor-specific transplantation antigens induced by selected DNA and RNA tumor viruses.

Major Findings: (1) In cooperation with Dr. Berge Hampar (NCI), the peroxidase staining technique for localization of murine gs antigen is being evaluated. The technique is both more sensitive and more specific than the fluorescent antibody technique. (2) Examination of early fetal hamster tissue for antigens shared with SV40-induced tumor cells has confirmed Coggin's findings that such a common antigen(s) exists, but does not support the concept that it is the important transplantation type antigen since it protects only male animals. His findings have been extended to show the embryos of primaparous females were effective immunogens against SV40 tumorigenesis while those from multiparous females were not. (3) Rescue attempts have been initiated employing human sarcomas and leukemias in a variety of combinations designed to activate latent viral genomes. These include co-cultivation and fusion with either BPL inactivated Sendai virus or lysolecithin.

Significance to Biomedical Research and the Program of the Institute: The treatment of cancer by immunologic methods has been an attractive hypothesis for decades, but it is only recently that new and fundamental discoveries in immunobiology have made cancer immunotherapy a real possibility. Many tumors possess individually distinct transplantation antigens against which the host mounts an immune response. The transplantation antigens of most virus-caused tumors in different animal species are the same for a given virus. The work being conducted by the contractor is part of a larger effort of the SVCP to isolate and test virus-induced tumor-specific transplantation antigens in animal model systems.

Proposed Course: (1) Improve use of the peroxidase reaction technique as a routine assay method for gs antigens and for intracellular localization of reverse transcriptase. (2) Study of the relationship of fetal antigen to transplantation antigen. (3) Attempt to rescue human oncogenic viruses using co-cultivation, fusion, and chemical activation with BrdU and IdU. (4) Continuation of attempts to prevent spontaneous tumors of mice by immunological techniques using direct immunization with vaccines, non-specific stimulation, and abrogation of tolerance to isogeneic tissues. (5) Continuation of attempts to immunize against neoplasia induced by known laboratory strains of oncorna viruses. (6) Continuation of attempts to purify transplantation antigen extracted by

high molarity salt solutions or neuraminidase treatment, and characterization of the isolated component(s).

Date Contract Initiated: February 1, 1971

Current Contract Level: $115,400

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
NIH-NCI-E-69-2007)

Title: Isolation and Purification of Transplantation Antigens

Contractor's Project Director: Dr. Donald F. H. Wallach

Project Officer (NCI): Dr. Charles W. Boone

Objectives: To investigate the biochemical and antigenic changes which occur at the cell surface during and after transformation by oncogenic viruses.

Major Findings: This program continued to search for new proteins in monkey kidney cells during early stages of permissive, lytic infection by the oncogenic DNA virus SV40. It relied heavily upon various methods of cell fractionation and upon polyacrylamide gel electrophoresis for visualizing the protein components of isolated cell fractions. Repeated experiments produced consistent protein patterns for uninfected cell fractions. The latest and best-controlled experiments show no new gel bands visible in fractions of infected cells if gels are stained in the Coomasie blue or Stains-All dyes. However, if the cells are labeled with glucosamine-1-^{14}C, microsome and microsome wash fractions of infected cells display at least one confirmed ^{14}C band not found in comparable fractions of control cells. The microsome "washes" were not innocuous rinses, but removed materials whose protein spectrum was different from the soluble fraction and whose ^{14}C specific activity was considerably higher. Inasmuch as by far the highest specific activity of any cellular component was found in the most buoyant microsome fraction, the activity of the material in the washes suggests that it is rich in membrane glycoprotein or in an export material which can be found on cell surface, or both. This "new" glucosamine-labeled component of microsomes from infected cells will be investigated further, using non-SVCP support.

Significance to Biomedical Research and the Program of the Institute: N/A

Proposed Course: This contract was terminated in September, 1971.

Date Contract Initiated: March 12, 1969

Current Contract Level: None

SALK INSTITUTE (NIH-NCI-E-72-3207)

Title: Growth Regulation of Normal and Transformed Cells and Immunological Approaches to Tumor Rejection and Prevention

Contractor's Project Director: Dr. Edwin S. Lennox

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: (1) Study how the surface of tumor cells differs from that of normal cells. (2) Attempt immunological prevention and rejection of tumors. (3) Study growth regulation of normal and cancer cells, as directed by serum factors.

Major Findings: This is a new contract and major findings have not yet been reported.

Significance to Biomedical Research and the Program of the Institute: The proposed contract focuses on the antigenic properties of cancer cells which are undoubtedly involved in the phenomena of unrestrained growth and metastasis of tumors. Projects A, C, and D work respectively towards an ultimate goal of enhanced immune rejection of tumors, regulation of tumor growth, and a chemical anti-tumor vaccine, any of which would be a major step forward in the control of human cancer.

Proposed Course: Project A. (Drs. Dulbecco & Lennox) Tumor cell lines with altered antigenic characteristics will be derived to test their ability to induce immune rejection of the parent tumor.

Project B. (Dr. Nicolson) The amount and distribution of cell surface antigens in normal and tumor cells will be studied using radioimmune assay, cytotoxic methods and especially EM visualization using ferritin-conjugated antibodies and plant lectins.

Project C. (Dr. Holley) The difference in the regulation of growth of normal and malignant cells by serum factors will be studied.

Project D. (Dr. Shier) Synthetic antigens will be prepared with chemical structure similar to that of the receptors on tumor cells responsible for agglutination with various plant lectins, and these antigens will be tested as immunogens to elicit anti-tumor cellular responses.

Date Contract Initiated: March 6, 1972

Current Contract Level: $398,640

BREAST CANCER VIRUS SEGMENT
Dr. W. Ray Bryan, OSD, DCCP, NCI, Chairman
Dr. Robert Depue, OSD, DCCP, NCI, Vice Chairman
Dr. Harry J. Clausen, OSD, DCCP, Executive Secretary

GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE (PH43-NCI-E-65-53)

Title: Human Breast Cancer Studies

Contractor's Project Director: Dr. William F. Feller

Project Officer (NCI): Dr. W. Ray Bryan

Objectives:

1. Continuation of studies on the association of virus-like particles in human milk, with human breast cancer.

2. Tissue culture attempts to propagate virus-like particles observed in human milk and breast cancer cells.

3. Attempts to induce mature virus production in established tissue culture lines of human cancers, particularly breast cancers.

Major Findings:

The most important result was the successful induction of virus production in human cancer cells in tissue culture by the method recently introduced by Rowe and associates for the activation of leukemia virus in mouse cells, namely by treatment with IUDR. The additional finding was made that treatment with DMSO following IUDR enhanced the reaction by a factor of 10 or more. The human cell cultures involved were established lines of a rhabdomyosarcoma, and of a metastatic lesion in a node of a patient with lung cancer. Virus particles were detected by electron microscopy. Whereas the particles observed in the lung cancer cells budded from cell membranes and in every way resembled the known C-type oncogenic RNA viruses, those of the rhabdomyosarcoma budded from the endoplasmic reticulum and were intracisternal rather than extracellular. Most of the particles resembled A-type particles but many of them had dense nucleoids and resembled C-type particles except for their intracisternal location. Further studies are in progress to rule out contamination of the cultures with some murine virus. If the latter are ruled out, this will represent the first successful induction of a human oncorna virus in an *in vitro* system.

Efforts to induce particle production in human breast cancer cultures by similar procedures have not been successful thus far.

In the studies on human milk, the new biochemical method of Spiegelman and Schlom for the detection of oncorna-type viruses has been introduced to replace the more time consuming and much less sensitive method of electron

microscopy. It involves the simultaneous test for 70 S RNA and reverse transcriptase. This method is now being used in the monitoring for selecting positive milks from which sufficient virus-type material can be recovered to support investigation directed toward propagating the agent in tissue culture.

Significance to Biomedical Research and the Program of the Institute:

This contractor was one of three initially selected to investigate the possible association of viruses with human breast cancer, and, in collaborative studies involving electron microscopic monitoring by another contractor (67-1176), was the first to show that particles resembling the oncogenic RNA viruses are present in milk of women who have had breast cancer.

This observation led to an expansion of the effort on breast cancer under the SVCP, and the studies under this contract are essential for determining whether the candidate agent being observed is actually virus, and related to the causation of the human disease.

Proposed Course:

The effort toward the objectives described will be continued at the current level.

Date Contract Initiated: 11/19/64

Current Annual Level: $171,400

HOWARD UNIVERSITY SCHOOL OF MEDICINE (NIH-NCI-E-70-2178)

Title: Immunological Studies on Human Breast Cancers and Other Neoplasms

Contractor's Project Director: Dr. Michael V. Viola

Project Officer (NCI): Dr. Ronald B. Herberman

Objectives:

1. Procurement of human specimens for use by SVCP participants as well as for research conducted in the contractor's institution.

   a. Selected specimens of breast and other cancers procured at operation or biopsy.

   b. Sera from patients with breast and other cancers, and from patients with non-neoplastic diseases for use as controls.

2. Establishment and characterization of tissue culture lines from selected cancer patients, particularly breast cancer.

3. Immunological studies of established cancer cell lines and of patients with breast cancer and other neoplasms.

Major Findings:

1. Procurement of specimens

   a. The following numbers of specimens have been distributed to 11 intramural and extramural participants of the SVCP.

Breast carcinomas	25
Fibrosarcomas	2
Gastrointestinal carcinomas	5
Lung carcinomas	2
Vulva carcinomas	3
Malignant effusions (breast cancer)	2
Lymphocyte preparations from Hodgkins patients	2
Lymphocyte preparation from breast cancer patient	1
Lymphocyte preparation from patient with CLL	1

   b.

Sera from breast cancer patients and matched controls	35
Sera from Hodgkins patients and matched controls	50
Selected cancer sera and controls	54
Large plasma specimens with high antibody titers against Be Lev cell line	2

2. Tissue culture studies:

   A cell line (W-1) has been established from a malignant pleural effusion from a patient with disseminated breast cancer. Using the simultaneous detection method, high molecular weight RNA (70 S) and reverse transcriptase were found in the concentrated supernatant from this cell line. It is now being further characterized, and cloned, for use in immunological and virological studies on human breast cancer.

3. Immunological studies of patients:

   Thirty-five patients with breast cancer and a similar number of controls have been studied with respect to lymphocyte response to various dilutions of PHA. Response to PHA decreased in disseminated breast cancer. The decrease was found not to be due to serum factor, and an attempt to correlate lymphocyte response to relative proportions of B and T lymphocytes is now in progress.

   Personnel from the contractor's laboratory are now being trained in the Project Officer's laboratory at NCI in several new immunological techniques to be employed in collaborative studies on breast cancer and other patients at the contractor's institution.

Significance to Biomedical Research and the Program of the Institute:

The NCI does not currently have an intramural program on the study of human breast cancer, and this university hospital in the Washington, D.C. area provides the important needs of (1) breast cancer patients for study by intramural scientists, in collaboration with the contractor; and (2) fresh cancer tissue, lymphocytes, and other specimens for tissue culture, immunological and virological studies both by intramural scientists and other SVCP participants.

Proposed Course:

Personnel from the contractor's laboratory are being trained in the Project Officer's laboratory at NCI for expanded immunological studies of cancer patients, particularly those with breast and colon cancers. An increase of about $6,000 in funding is projected.

Date Contract Initiated: 4/27/70

Current Annual Level: $49,729

INSTITUTE FOR MEDICAL RESEARCH (PH43-NCI-E-68-1000)

Title: Studies of Human Milk and Mammary Tumors

Contractor's Project Director: Dr. Dan H. Moore

Project Officer (NCI): Dr. W. Ray Bryan

Objectives:

To explore human milk and breast cancer tissue in search of a virus that might be etiologically related to the disease.

Major Findings:

As previously reported, important leads suggesting the possible involvement of a virus in human breast cancer were obtained in exploratory studies, namely: (1) the finding of virus-like particles resembling the oncogenic RNA viruses in some milk specimens from women belonging to high-breast-cancer families, and (2) the finding of reverse transcriptase activity in such particle-positive milks (initially collaborative with contract #70-2040).

A multidisciplinary effort was initiated at the beginning of this contract year to follow-up these leads on the human problem and to use the mouse mammary tumor virus (MTV) system to guide the human studies.

A biochemical laboratory was added and 25 human milk specimens studied thus far show that about one-third of them were positive for reverse transcriptase, confirming the earlier exploratory results. In other biochemical studies the

five major proteins of purified mouse MTV recently reported by Nowinski have been confirmed, and an additional protein has been identified in the 69,000-110,000 molecular weight range which is thought to be the enzyme, reverse transcriptase.

New techniques developed in the expanded tissue culture laboratory have resulted in the successful explanation of 71 human breast cancers. Forty-five have been investigated thus far by negative staining and thin section electron microscopy. Spiked particles resembling the MTV have been found in 3, and smooth surfaced particles resembling C-type virus have been found in 24. A third type of particle with shorter spikes than the MTV was found in 8 cultures. Double blind studies are in progress to determine the association of reverse transcriptase with type of particle. A total of 172 milk specimens have been collected for this purpose from women of high-breast-cancer risk and control populations.

Neutralization tests have been initiated on 60 human sera (from breast cancer patients and controls) to determine whether they reduce the activity of MTV in test mice. Other immunological studies underway include: (1) the immunization of rabbits with high-speed pellets from human milk containing high reverse transcriptase activity and a high number of virus-like particles, as a source of specific antibody against the candidate human particles; and (2) the immunization of test mice with such human candidate virus to determine whether it will protect against later challenge with the mouse MTV.

Significance to Biomedical Research and the Program of the Institute:

This was one of three projects initially set up to determine whether sufficient evidence could be found for an association of virus with human breast cancer to justify a broader formal program on the virus approach to the etiology of the human disease. The results of studies under this and other related contracts (see also PH43-NCI-E-65-53 and PH43-NCI-E-67-1176) led to an expansion of programmed activities on breast cancer under this as well as the other contracts.

Proposed Course:

This multidisciplinary effort will continue at its current level for further electron microscopic, biochemical, tissue culture, and immunological investigations of the candidate human virus in milk and breast cancer tissue.

Date Contract Initiated: 6/28/68

Current Annual Level: $402,000

MASON RESEARCH INSTITUTE (NIH-NCI-E-70-2204)

Title: Hormonal Influences on the Induction of Breast Cancer in Specific Virus Infected Animals

Contractor's Project Director: Dr. Marcus M. Mason

Contractor's Principal Investigator: Dr. Arthur E. Bogden

Project Officer (NCI): Dr. W. Ray Bryan

Objectives:

(1) By studies of the hormone profiles of blood and urine of experimental animals during normal physiological cycles and during different regimens of hormone treatment, to determine the hormone dosages, combinations, and sequences to be tested in the virus-hormone co-carcinogenesis studies of objective (2).

(2) To determine whether candidate viruses isolated from animal breast cancers are capable of inducing breast cancers in their natural hosts and/or animals of other species, using appropriate hormone stimulation of the hormone-dependent target tissues (mammary glands). Candidate viruses currently under investigation are: (a) the Mason-Pfizer Monkey Virus (M-PMV) isolated from a breast cancer of a Rhesus monkey at the contractor's institution; and (b) the R-35 virus isolated from a transplant of a spontaneous breast cancer of a Sprague-Dawley rat, also at the contractor's institution.

Major Findings:

M-PM Virus

The appropriate regimens for hormonal treatment (hormones, dosages, sequences and combinations) have been worked out in female Rhesus monkeys for (1) producing hypertrophy of the breasts with hyperplasia of the ductular and alveolar epithelium, and (2) for inducing and maintaining lactation of such stimulated mammary glands. These regimens are now being applied in two types of investigations: (1) Hormone treatment of female monkeys inoculated as newborns with M-PMV. Treatment is begun when they reach 18 months of age and will be continued for prolonged periods as a co-factor in breast tumor induction. The animals will be observed for two to three years for the appearance of breast cancers. (2) Inoculation of sexually mature, hormone treated, female Rhesus monkeys with M-PMV directly into the hyperplastic ductules and alveolar tissues to determine their susceptibility to infection with M-PMV. Infectivity is currently being tested by inducing lactation and examining milk for C-type M-PMV particles, reverse transcriptase activity (collaborative with others), and the presence of specific viral antigens. These studies are at an early stage and sufficient results are not available for evaluation at this time.

R-35 Virus

Until recently, no rapid in vitro method was available for determining the biological activity of this virus, and the fact was not previously known that its biological potency is greatly diminished by freezing and storage.

In experiments initiated with frozen virus, before this information became available, the following results have been obtained:

A total of 5 female Sprague-Dawley rats inoculated as newborns with the R-35 virus have developed mammary adenocarcinomas among a total of 98 inoculated; giving an overall incidence of 5.1%. The time of appearance varied from 4 to 14 months, all but 1 appearing in rats less than one year of age. No tumors of this type were observed among 197 uninoculated controls within the same experiments.

All of the mammary adenocarcinomas occurred in rats inoculated with 3 of the 9 different lots of frozen virus used in the studies, with the following frequencies: 2/36 (5.6%), 2/16 (12.5%), and 1/20 (5.0%). No tumors of this type occurred among animals inoculated with the other 6 lots of frozen virus.

Another type of tumor, fibroadenoma, known to occur spontaneously in older animals of this strain has been observed in two uninoculated control animals at approximately 11 months of age.

Although the small number of mammary tumors observed does not represent definitive evidence that the R-35 virus is oncogenic for rat mammary tissue, the results lend strong encouragement to this possibility. These studies are now being repeated with fresh virus inoculated on the same day as it is prepared, which should have much stronger biological activity.

Significance to Biomedical Research and the Program of the Institute:

At the present time, breast cancer is known to be caused by a virus in only one animal species, the mouse. This project, involving biological testing of candidate viruses for oncogenicity, is part of a broader program activity for determining whether viruses are related to breast cancer in animals other than mice. Such animal studies are necessary for developing technology and approaches to the study of the human breast cancer virus problem.

Proposed Course:

The experiments under way will be continued until the planned numbers of experimental animals have been inoculated with virus (50 monkeys, 2000 rats, and several hundred each of mice and hamsters, all inoculated as newborns). Observations for tumor induction will be continued for the lifetimes of the rodents, and for 2-3 years in the case of monkeys. If oncogenicity is demonstrated for any candidate virus, systematic follow-up studies will be introduced.

Date Contract Initiated: 6/9/70

Current Annual Level: $265,000

MEDICAL COLLEGE OF WISCONSIN (PH43-NCI-E-68-1010)

Title: Hormone Effects on Virus Particle Activity in Breast Cancer

Contractor's Project Director: Dr. Ronald Pattillo

Project Officer (NCI): Dr. Robert H. Depue, Jr.

Objectives:

To study the effects of human hormones on possible oncogenic virus production in human breast cancers in vitro. The hormones to be studied include the lactogenic hormone and biologically active estrogenic and progestational steroids.

Major Findings:

A series of breast tumors have been studied in the initial experiments to define culture conditions, optimum type of tumor-hormonal responsiveness and potential for continued growth in culture. Encouraging new leads that may have relationship to the recently reported identification of virus particle production within epithelial "domes" from mouse mammary tumors have been observed in one of the human tumor cultures. Attempts to subculture these "focus" appearing cell aggregates have not as yet been successful. However, these experiments suggest a possible parallel between mouse mammary tumor behavior in vitro and the human tumor. The culture medium is modified by conditioning with the hormone secreting trophoblast cells in vitro. This medium also contains polyvinylpyrrolidine which favors the growth of tumor cells in suspension. Several of the tumors show epithelial cells which appear morphologically similar to breast cancer cells. In the cultures, to date, insufficient cells are available for testing for functional markers such as casein or the production of B-particles.

Significance to Biomedical Research and the Program of the Institute:

The contractor has recently established a multipotential human hormone synthesizing trophoblastic cell system which is used in co-cultivating experiments under a variety of conditions aimed at providing suitable hormone conditions for human breast cancer cell propagation. These studies may provide an important insight into the hormonal effects on virus activity in human breast cancer.

Proposed Course:

The effort toward the objectives stated will be continued at the current level.

Date Contract Initiated: 9/19/63

Current Annual Level: $111,635

MEMORIAL HOSPITAL (NIH-NCI-E-71-2194)

Title: Procurement of Human Serum Specimens from Defined Population Groups for Immuno-epidemiological Studies

Contractor's Project Director: Dr. Herbert F. Oettgen

Project Officer (NCI): Dr. Harry J. Clausen

Objectives:

Procurement of serum specimens from the following defined population groups as a part of a collaborative effort to determine whether candidate viruses isolated from human or animal sources are related etiologically to human breast cancer.

Basic defined population: Women entering Memorial Hospital, New York City, for first diagnosis of any breast disease.

Test group: Women whose lesions prove to be malignant as determined by biopsy.

Control groups:

a. Women whose lesions are found on biopsy to be benign proliferative reactions or reactions suspected as being pre-neoplastic in nature.

b. Women whose lesions are considered to be unrelated to neoplasia.

Major Findings:

This contract was negotiated 6/23/71, but there was a 6-month delay in activating it because laboratory space to be occupied did not become available until January. The previous occupants were unable to vacate because their new quarters could not be made ready for occupancy due to a strike in New York City. Since there was a delay in starting the activities under this contract the serum specimen procurement did not start until April.

Significance to Biomedical Research and the Program of the Institute:

Since viral agents suspected of causing cancer in man cannot be tested directly in human subjects, it is necessary to establish etiological relationship indirectly through immuno-epidemiological studies. This contract is for procuring the epidemiologically defined bank of serum specimens essential to the determination of whether antibodies against suspect viruses occur with higher frequency, and in larger amounts, in sera of women with breast cancer as compared with appropriate controls.

Proposed Course:

It is anticipated that a sufficiently large bank of specimens for the proposed sero-epidemiological studies can be acquired under this contract within a period of 2 to 3 years.

Date Contract Initiated: 6/23/71

Current Annual Level: $46,340

MICHIGAN CANCER FOUNDATION (NIH-NCI-E-71-2421)

Title: Studies in High Breast Cancer Families

Contractor's Project Director: Dr. Michael J. Brennan

Project Officer (NCI): Dr. Harry J. Clausen

Objectives:

The first year of this contract was a feasibility study to determine:

(a) If large quantities of human milk containing sufficient virus-like particles could be secured through monitoring large numbers of milk specimens taken from lactating patients on obstetrical services in the Detroit metropolitan area and to establish demographic genetic characterizations of these patients' families so as to determine the strength of the genetic or nongenetic factors which might be associated with virus-like particle secretion in the milk.

(b) Whether electron microscopy, through negative staining procedures, represented an adequate method of monitoring milk specimens, and the selection of those which contained relatively large amounts of virus-like particles.

Major Findings:

Collections of milk samples are underway at 31 of the 43 obstetrical services in the area and currently milk specimens are being obtained from some 150 nursing women per month. Objective information on the causes of death and neoplastic disease experience is now complete for 70 families and partially completed for another 100 families. Therefore, the operational base upon which large-scale studies of a fully demographic spectrum of young nursing mothers has been established and the characteristics can now be developed in relation to breast cancer etiology and development.

Some 335 milk specimens have been shipped to NCI as well as other investigators involved in the Special Virus Cancer Program. To date few, if any, fully typical B particles have been demonstrated. By means of negative staining electron microscopy milk specimens have been found which contain particles of a virus-like appearance but not fully meeting the criteria for

"B" particles. It is felt that particles are being destroyed by a milk component and further work on particle preservation is being continued.

Significance to Biomedical Research and the Program of the Institute:

At this time, breast cancer is known to be caused by a virus in only one animal species, the mouse. Therefore, studies based on leads from this animal species have been conducted to determine if evidence might be obtained for an association of viruses with human mammary cancer. The "clustering" of breast cancer within family groups and its similarity to that observed for mouse mammary cancer before the development of inbred mouse strains has suggested that a virus might also be involved in human breast cancer. Efforts to obtain additional evidence on a basis of which virus-like particles in human milk might be demonstrated to be actual virus are in progress.

Proposed Course:

Since large scale monitoring of human milk specimens with negative staining EM alone has not proven satisfactory, it is proposed that the primary monitoring will be done in the future with new biochemical techniques that have recently become available, namely the simultaneous test for 70 S RNA and reverse transcriptase. EM will be used only for confirmation on those milk specimens that prove to be positive for reverse transcriptase and 70 S RNA. These monitoring and investigative procedures on milk samples will be conducted in the contractor's laboratory as well as the study of medically indicated biopsy material and lactating mammary tissue from collaborating donors. Furthermore, studies on methods for preserving the morphological integrity and enzyme activity of the virus-like particles in milk samples will be continued.

Date Contract Initiated: 6/20/71

Current Annual Level: $119,000

PFIZER INC. (PH43-NCI-E-67-1176)

Title: Virological Studies of Human and Animal Breast Cancers

Contractor's Project Director: Dr. K. E. Jensen

Project Officer (NCI): Dr. W. Ray Bryan

Objectives:

1. Electron Microscopic Studies

   An electron microscopic laboratory with professional and supporting staff is operated for two purposes: (a) The search for viruses in human and animal breast cancers, in collaboration with other SVCP

participants not having this capacity; and (b) EM monitoring and research at the contractor's institution associated with virological studies on new candidate viruses isolated from breast cancer (see objective 2).

2. Virological studies directed toward the further characterization of new candidate breast cancer viruses, and the development of new animal model systems for guiding research on the human problem.

Major Findings:

Previous studies involving the EM collaboration of this contract have resulted in the finding of virus-like particles resembling known oncogenic RNA viruses in the milk of women who have had breast cancer, and the discovery of two new candidate viruses isolated from breast cancers of animals--the Mason-Pfizer Monkey Virus (M-PMV) and the R-35 rat virus (R-35V). The successful propagation of the latter two animal viruses, in collaboration with another contract at the contractor's institution (70-2080), led to the supplementation of this contract during the current year to provide a facility specifically for the study of breast cancer viruses, and to carry out systematic studies on the R-35 and M-PM viruses.

The following additional results have been obtained:

R-35V

This virus has been found to infect and transform normal lactating rat mammary gland cells in tissue culture. The reaction appears to be specific for mammary tissues since other types of rat cells (e.g. spleen, thymus, bone marrow, kidney) were neither infected nor transformed. An in vitro assay method based upon focal transformation of the susceptible cells has been developed and is now being used in systematic virological studies.

Evidence that the R-35 virus is oncogenic is represented by the fact that transplants of foci transformed in vitro to weanling rats grow as highly malignant tumors. The latter contain both carcinomatous and sarcomatous components.

The virus has been found to contain gs 3 antigen but not the gs 1 antigen of any of the mouse oncogenic viruses.

M-PMV

An immunofluorescent end-point assay has been developed for the in vitro assay of the M-PMV in NC-37 cells (of human origin) which it has been found to infect.

Specific antigens of the M-PMV have been observed in 2 of 5 normal Rhesus monkey embryos tested, indicating that this virus might be indigenous in this species.

Immunological studies have shown that the M-PMV virion contains five distinct antigens, three associated with the coat and two with the core, or nucleoid.

Significance to Biomedical Research and the Program of the Institute:

The contractor's EM laboratory continues to be a key participant in a broad collaborative program in the search for viruses related to human and animal breast cancers.

The further research and development on the two new candidate animal breast cancer viruses in the contractor's laboratory is essential to the application of these new models to studies of the possible viral etiology of human breast cancer.

Proposed Course:

The activities described will be continued at the current level until the determination is made whether these candidate animal viruses are etiological agents of breast cancer of the types from which they were isolated.

Date Contract Initiated: 6/28/67

Current Annual Level: $328,000

TEL AVIV UNIVERSITY (NIH-NCI-E-72-3237)

Title: Isolation, Purification and Propagation of Virus-like Particles from Human Milk in Israel

Contractor's Project Director: Dr. Jafa Keydar

Project Officer (NCI): Dr. Timothy E. O'Connor

Objectives:

Purification of candidate virus from various milk samples obtained from women of designated high-breast-cancer-risk populations in Israel and assay for RNA-instructed DNA polymerase as well as attempts to grow the milk "virus" in human tissue cultures.

Major Findings:

This contract was initiated late in the fiscal year (March, 1972) and although work toward the stated objectives is fully under way, it is too early to assess the significance of apparent progress already being made.

Significance to Biomedical Research and the Program of the Institute:

Israel is a particularly favorable setting for an investigation of this type since high-risk donors of milk are easy to identify and line-up for milk studies

well in advance of delivery, because of the following reasons: (a) Israel has a mandatory national cancer registry and the occurrence of breast cancers within families can be readily determined, (b) Israel has a national health plan which includes maternity cases who report for care early in pregnancy, allowing ample time for surveys for cancer history, (c) most women deliver in hospitals thus simplifying the logistics of milk procurement, and (d) most importantly, there are several ethnic groups within Israel having breast cancer risks among the highest known.

The evidence of virus-like material in human milk obtained in other SVCP projects makes it essential to propagate this candidate agent for further characterization and determination of its association with human breast cancer. This contractor has unique advantages for pursuing these goals.

Proposed Course:

The project will be continued for at least two years at essentially the same level.

Date Contract Initiated: 3/23/72

Current Annual Level: $71,750

UNIVERSITY OF CALIFORNIA, DAVIS, CALIF. (NIH-NCI-E-72-2080)

Title: *In vitro* cultivation of human and mouse mammary tumor viruses

Contractor's Project Director: Dr. Robert D. Cardiff

Project Officer (NCI): Dr. Robert H. Depue

Objectives:

1. To study human breast tissue under various experimental conditions developed from the mouse mammary model for the presence of possible human mammary tumor viruses.

2. To study the production of mouse mammary tumor virus (MTV) *in vitro* in order to develop concepts, techniques, and reagents that might be applicable to larger scale production of this virus and of potential human breast cancer viruses.

Major Findings:

This contract (negotiated February 1, 1972) is still in the early stages of implementation and although tissue culture studies on both human and mouse tissues are in progress, no experiments have yet been completed.

Significance to Biomedical Research and the Program of the Institute:

The finding of virus-like particles as well as 70 S RNA and reverse transcriptase in human milk and breast cancer tissue cultures by several investigators within the SVCP strongly suggest that a virus may be associated with human breast cancer. If so, it will be necessary to produce such virus in large quantities in vitro to further characterize it and determine its relation to the human disease. But this problem, in vitro cultivation, has not yet been solved for the mouse MTV.

This contract is for the development of knowledge and technology for in vitro cultivation and large scale production of the MTV, with simultaneous application of progress to attempts to cultivate the human candidate virus.

Proposed Course: No change in initial contract.

Date Contract Initiated: 2/1/72

Current Annual Level: $99,376

NETHERLANDS CANCER INSTITUTE (NIH 72-3260)

Title: Immunogenetic Studies on Breast Cancer and Leukemia

Contractor's Project Director: Dr. L. M. Boot

Contractor's Assistant Project Director: Dr. J.H.M. Hilgers

Project Officers (NCI): Dr. W. Ray Bryan and Dr. Walter E. Heston

Objectives: To study the transmission of mammary tumor virus in the GR strain of mice through segregation experiments to determine whether mammary tumor development is due to a single genetic locus, giving further evidence for the provirus theory.

Major Findings: This is a newly funded contract and there are no findings to be reported.

Significance to Biomedical Research and the Program of the Institute: Epidemiological studies on human breast cancer indicate that in families having a high risk to this disease, the genetic factor associated with the higher risk is transmitted through the paternal as well as the maternal line. The GS strain of mice to be studied under this contract has this type of inherited disease, in contrast to the C_3H strain in which the predominant influence in the high incidence of breast cancer is transmission of the mouse mammary tumor virus (MTV) through the mother's milk. Although MTV is also transmitted through the mother's milk in the GS strain, foster nursing of the young on low breast cancer strain females does not reduce the excess risk as it does in the C3H strain. The GR strain may therefore represent a more appropriate animal model for leading studies on the human disease. The GS strain is not now being adequately studied, and more work on it is needed because of the popular question now being raised whether non-nursing of female infants, by mothers belonging to high risk populations, should be practiced. If the human situation is more like that in GR mice, then obviously non-nursing would have little or no effect in reducing risk in the human disease.

Proposed Course: The GR strain of mice developed by Muhlbock is a unique strain for the study of the cause and development of mammary tumors. By an early age practically all the females have mammary tumors which have arisen from premalignant hormone responsive plaques. These tumors are caused by the mammary tumor virus (MTV)--the tumors have B particles--but the virus is transmitted vertically apparently through germ cells, as a genetic factor is transmitted. It is on this that Bentvelzen developed his concept of the "provirus" in its transmission. Segregation studies have suggested that susceptibility to mammary tumor development in this strain is due to a single dominant gene, presumably the same segment of the genome from which the virus arises. They now have two rapid tests--one for microscopically small tumors that requires three weeks and indicates the presence of MTV, and an immunofluorescence test of mammary cells that can be done in a day and indicates the presence of MTV antigen.

Using both these tests for classifying mice of segregating populations they propose to confirm that this is a single locus and then to locate it in the genome. This will be done with linkage tests using linkage stocks from Bar Harbor that carry many of the usual markers and also a number of biochemical markers. Next they propose to develop congenic strains, one of strain GR with the allele at this locus from $C_{57}BL$, one of strain $C_{57}BL$ with the tumor gene from GR, and one of strain O_{20} with the tumor gene from GR.

These are the next logical steps in the study of the transmission of this tumor virus. They should provide proof of the single genetic locus and give further evidence for the provirus theory. In addition, the congenic lines will be needed for future work.

It is also proposed to do the same thing with the mouse leukemia virus system as a control for the MTV-mammary tumor studies.

They then want to test for type specific antigens of C_3Hf_{MTV}(NIV) and GR MTV and see if these can be identified in segregating backcross mice and correlated with the occurrence of mammary tumors. We need any further clarification of these lines of virus that we can get.

With the anti-MTV and anti-MuLV sera developed for these viral-genetic tumors they are also proposing to screen human tumors for possible inter-species antigens. These studies would be correlated with EM scanning of the tumors for viral particles.

Date Contract Initiated: June 28, 1972.

Current Funding Level: $60,000

TUMOR VIRUS DETECTION SEGMENT

Dr. George J. Todaro, Chief, VLLB, DCCP, Chairman
Dr. Bernard Talbot, VLLB, DCCP, Vice Chairman

CALIFORNIA SCHOOL OF MEDICINE, UNIVERSITY OF (NIH-72-3236)

Title: Effect of Oncogenic Viral Transformation on the Regulation of Gene Expression in Cultured Mammalian Cells

Contractor's Project Director: Dr. Gordon M. Tompkins

Project Officer (NCI): Dr. Bernard Talbot

Objectives: To study growth regulation in normal mammalian cells and the loss of regulation on transformation.

Major Findings: This is a new contract and major findings have not been reported.

Significance to Biomedical Research and the Program of the Institute: In tissue culture, a variety of growth producing agents (e.g., serum, insulin, cycloheximide) lead to a coordinated set of cellular responses. This set includes increased rate of protein synthesis, decreased rate of protein degradation, increased rate of tRNA and rRNA synthesis, aggregation of polysomes, increased rates of uptake and phosphorylation of nucleic acid precursors, and increased rate of glucose transport. These cellular responses to growth producing agents have been named the "pleiotypic growth program" by Dr. Tomkins; he suggests that it is mediated by a single underlying effector molecule analogous with the "stringent response" in E. coli, and that the growth producing agents initiate the pleiotypic growth program by reacting with receptors at the cell membrane.

Preliminary data indicate that mammalian cells transformed by DNA oncogenic viruses are permanently "switched on" for the pleiotypic growth program and are thus unresponsive to exogenous growth regulators. By studying this phenomenon, the contractor may discover why malignant cells do not respond to normal control mechanisms; i.e., how viral transformation converts cells from responsive normal to unresponsive malignant. Ultimately, such knowledge may lead to control of malignant cell growth.

Proposed Course: (1) In normal cells, a study of how growth promoting agents interact with the cell membrane to trigger the pleiotypic response, identification of the pleiotypic effector, which may be cyclic AMP, and a study of its biochemical mechanism of action. (2) In virally transformed cells, a study of the alterations in the cell membrane which affect the pleiotypic response.

Date Contract Initiated: April 25, 1972

Current Contract Level: $72,430

UNIVERSITY OF CALIFORNIA AT LOS ANGELES (NCI-E-72-3226)

Title: Search for Presence and Distribution of Hybridizable Tumor Virus DNA in Tissues from Cancer Patients.

Contractor's Project Director: Dr. Marcel Baluda

Project Officers (NCI): Dr. George J. Todaro and Dr. Roy F. Kinard

Objectives: To provide evidence that human cancer is caused by RNA viruses by showing that DNA in cells of human cancer patients can be hybridized with the RNA genome of tumor viruses. For this purpose a bona fide human oncorna virus or an animal virus, perhaps from a primate, which is partly homologous to human virus is needed. Therefore, efforts will be initially aimed at obtaining radioactively labelled RNA from such viruses and testing their hybridizability with DNA extracted from human tumors.

Major Findings: None reported. This contract has been in effect too short a time to expect significant results.

Significance to Biomedical Research and the Program of the Institute: This unique and imaginative approach may provide strong evidence that human cancer is caused by viruses and may provide support for the oncogene theory. In order to devise effective therapy for cancer, it is essential to determine whether the viral DNA is present only in the tumor cells, in the surrounding tissue, or in all the cells of the cancer patient. Such a study will provide information on the mode of infection and epidemiology of these viruses, thereby making possible the development of prophylactic and therapeutic measures. For instance, if all the tissues from a cancer patient contain viral DNA, it would appear that the patient came from an "infected" germ cell or became infected in utero.

Date Contract Initiated: June 8, 1972

Current Contract Level: $118,900

HARVARD UNIVERSITY (NCI-E-72-3246)

Title: Research on Herpesviruses Causing Lymphoma in Primates

Contractor's Project Director: Dr. Luis Melendez

Project Officer (NCI): Dr. Roy F. Kinard

Objectives: To further characterize a new oncogenic herpesvirus, Herpesvirus ateles and determine its pathogenicity in primates and other animal species; to determine if H. saimiri (attenuated) can be employed to prevent the malignant lymphoma induced by the virus; to determine if several new herpesvirus isolates obtained from South American monkeys are oncogenic in non-human primates.

Major Findings: None. The contract was signed too recently.

Significance to Biomedical Research and the Program of the Institute: The knowledge gained in the study of these lymphomas produced by herpesviruses may provide an insight into the understanding of similar malignant processes of man in which herpesviruses are considered as likely candidates for etiology: Epstein-Barr virus (EBV) in Burkitt's lymphoma, and Herpes simplex type 2 in carcinoma of the cervix.

Date Contract Initiated: June 26, 1972.

Current Contract Level: $72,650

ATOMIC ENERGY COMMISSION (NIH-NCI-E-[FS-13])

Title: Co-carcinogenesis Program

Contractor's Project Directors: Dr. F. T. Kenney
Dr. G. D. Novelli
Dr. M. G. Hanna
Dr. R. L. Tyndall
Dr. R. W. Tennant

Project Officers (NCI): Dr. James T. Duff
Dr. Timothy O'Connor

Objectives: In January 1963 an interagency agreement was established between the National Cancer Institute and the Oak Ridge National Laboratory for carcinogenesis studies. During the past 3 years the agreement has been funded by both the Carcinogenesis and Viral Oncology (SVCP) Program Areas of NCI. Only the SVCP funded portion is reported here. The broad objectives are (1) to study the interaction of RNA tumor viruses with the host immune mechanism (Hanna); (2) to conduct investigations on the biochemical mechanisms involved in the initiation of cancer (Novelli); (3) to provide fundamental understanding of the mechanisms by which gene expression is regulated in mammalian cells (Kenney); (4) to investigate the commonality between embryogenesis and oncogenesis and its possible significance in the control of cancer (Tyndall); and (5) to study the functional and antigenic properties of cells infected or transformed by murine RNA tumor viruses, and the nature of the interactions between cells, viruses, and carcinogens (Tennant).

Major Findings: An improved method of isolating reverse transcriptase from spleens infected with Rauscher leukemia virus has been developed. The quantity of reverse transcriptase isolated from the microsomal fraction of a gram of infected spleen is equivalent to that obtained from 0.4-0.8 ml of a 10X virus concentrate from mouse plasma, indicating the superiority of infected spleen as a source of the enzyme.

The optimal reaction conditions for reverse transcriptase from Rauscher leukemia virus (RLV) apparently differ from those for the same enzyme isolated from avian myeloblastosis virus (AMV), regardless of the template used. Other significant differences are: the AMV transcriptase is larger than the RLV enzyme, and is more resistant to inhibition by poly(U) or Poly(G); the purified RLV enzyme is quite stable, whereas purified AMV form is very labile. For the RLV enzyme, optimal conditions differ markedly depending on the template used in the reaction mixture. For example, Mg^{++} is the preferred ion in the DNA-dependent system, while Mn^{++} is much less active for DNA-dependent activity but is absolutely required for RNA-dependent activity. The polymerase has a tenfold higher affinity for ribopolymers than for deoxyribopolymers.

Recent studies with 90% pure, Type A particles from mouse plasma-cell tumors support the idea that these particles do not contain reverse transcriptase.

Electron microscopic examination of myeloma tumor cells from BALB/c mice previously infected with RLV and bearing transplanted myelomas revealed budding Type C particles, suggesting that myeloma blast cells, like immunoblasts in the spleen, are very susceptible to RLV infection.

Polyadenylic acid [poly(A)] reproducibly inhibits Moloney virus replication in cultured mouse cells, but only when added before or during the first 4 hours of infection. Poly(U) and poly(C) were inactive while poly(G) was cytotoxic. The inhibition by poly(A) is not due to any observable effect on growth and division of the host cells. This finding supports the interpretation that the effect of poly(A) on leukemia virus replication is due to the specific inhibition of viral DNA synthesis.

The restrictiveness of human cells for mouse leukemia virus replication was investigated by cell fusion techniques. Virus synthesis could not be detected in human cells or in human-mouse heterokaryons, but did occur in mouse cell synkaryons. These results suggest that the nonpermissiveness of human cells for Moloney leukemia virus (MoLV) is dominant. Five cloned cell lines of human-mouse hybrids, containing less than the full complement of human chromosomes, were also tested for permissiveness to MoLV, and were found to be receptive to virus synthesis, suggesting that some human gene(s) act to inhibit replication of the virus. Attempts to correlate this nonpermissiveness of human cells with a specific chromosome are underway.

In a previous study, immunization with mouse fetal cells suppressed the growth of both plasma cell tumors and spleen cells infected with Rauscher leukemia virus, suggesting a cross-reactivity between fetal cells and the two types of tumor. To establish true cross-reactivity, it was necessary to demonstrate the reciprocal of the above (that is, suppression of fetal cells after immunization against the tumors). An *in vivo* assay for quantitating immunization against injected cells was developed, based on the colony-forming units (CFU) test in the spleen. With this assay, it was shown, for the first time in an *in vivo* system, that fetal cells are indeed suppressed in mice immunized with plasma cell tumors. This

demonstration, coupled with the reciprocal finding is compelling evidence that fetal cells and plasma cell tumors have common cell-surface antigens.

Significance to Biomedical Research and the Program of the Institute: This effort is focused on the phenomenon of carcinogenesis, considering this as a fundamental biological problem with common features whether the carcinogenic stimulus be a chemical, or radiation, or a virus. Special attention, however, is given to particular areas such as carcinogenesis and cocarcinogenesis in the respiratory tract and the role of both Type C viruses and cellular control mechanisms in murine leukemias.

Proposed Course: Continue to develop a concerted, interdisciplinary research program in the central aspects of both chemical and viral carcinogenesis.

Date Contract Initiated: July 1, 1963 (Viral Oncology Funding: July 1, 1970)

Current Contract Level: $1,000,000

UNIVERSITY OF WISCONSIN (NCI-E-72-2022)

Title: Role of RNA tumor viruses and related genetic information in induction of tumors by chemicals.

Contractor's Project Directors: Dr. Charles Heidelberger
Dr. James Miller

Project Officers (NCI): Dr. Roy Kinard
Dr. George Todaro

Objectives: To induce neoplasia in mice and rats *in vivo* and transformation of mouse and rat cells *in vitro* and determine the degree of viral activity in this process by immunological techniques, DNA-RNA hybridization and tests for polymerases.

Major Findings: Breeding colonies of 13 inbred strains of mice and two inbred strains of rats have been established to serve as a source of all the test materials to be used under this contract. The following mouse strains are now in production: C57Bl/6, Balb/c, 1, 129, AKR, C58, NZB/Bl, C3Hf/Bl, DBA/2, C3H/An, A, Rlll, and GR. The inbred rat strains are W/Fu and BN. Mice of these strains are regularly being provided for the chemical induction of tumors. Groups of each of these strains have been injected subcutaneously with either 250 µg of 3-methylcholanthrene (MCA) in 0.1 ml of trioctanoin or with the solvent alone.

The mouse breeding colony has also been utilized as a source of cells for *in vitro* carcinogenesis studies. Six lines of cells have been obtained from the prostates of individual C3H mice; 3 from anterior prostates, and 3 from ventral prostates. Selected clones derived from these lines are now being tested for malignant transformation using MCA, MCA-epoxide, and N-methyl-N'-nitro-nitrosoguanidine (MNNG).

Lines of mouse embryo cells similar to the original 3T3 Swiss mouse embryo cell line have been established from C3H and AKR mice. These lines have characteristics similar to the original 3T3 line -- in particular, a low saturation density. Clones derived from these lines are now being tested for chemical transformation. A 3T3 line will also be initiated from C57B1 mice for comparative transformation experiments.

Significance to Biomedical Research and the Program of the Institute: The exhaustive yet inconclusive search for oncogenic viruses in human tumors, and in many kinds of tumors in other animals, has turned attention toward the detection of viral genetic information in the form of RNA or DNA or both, which codes for oncogenic RNA viruses or portions thereof. This project is designed to assess the types of tumors in laboratory animals in which viral information is important to the induction of malignancy by chemicals. The objective is to provide a guide to the solution of etiology of human tumors, which is one of the prime targets of the SVCP.

Proposed Course: Continuation as described.

Date Contract Initiated: September 1, 1971

Current Contract Level: $249,500

UNIVERSITY OF MINNESOTA (NCI-E-71-2261)

Title: Tumor Viruses in Immunological Deficiency Diseases of Man

Contractor's Project Director: Dr. Robert A. Good

Project Officers (NCI): Dr. George Todaro
Dr. Roy Kinard

Objectives: To clarify the role of immunologic surveillance, cellular and humoral factors and genetic factors in protection against neoplasia; to search for viruses in patients with premalignancy and on immunosuppressive therapy.

Major Findings: New methods for evaluation of the clinical status of patients with immunodeficiency syndromes and malignancy have been developed. These laboratories can carry out efficiently all of the immunological testing recommended for immunodeficiency patients by the World Health Organization Expert Committee.

Successful explantation of a very high percentage of human tumors has provided material for other SVCP contractors for immunologic and virologic analysis. In nine months of the first contract year they

have successfully explanted 132 tumors, and of these, 54 have been sent to Meloy Laboratories and are available to other contractors on request. Of special interest is a cell strain derived from a patient with an embryonal rhabdomyosarcoma which is currently in its 15th passage.

In the past nine months, skin biopsies have been obtained from additional high cancer risk immunodeficient patients bringing the total number to 33. To date 15 of these have been tested. Cell strains from 14 to 15 patients were found to have low or normal susceptibility to SV40.

Successful explantation of a high percentage of tumors has provided material for evaluation of cell-mediated and humoral immune response of patients to their own as well as histologically identical tumors. In addition to confirming the presense of cell-mediated immunity directed against tumor cells in patients with neuroblastoma and rhabdomyosarcoma, they have demonstrated cell-mediated immunity and serum mediated "blocking" of the cellular response in one patient with lymphosarcoma and another with malignant teratoma.

A new direct culture method for analyzing phytohemagglutination responses of circulating leukocytes which promises to permit quantitation of the number of responding T-cells has been developed and is being tested.

The facilities for evaluating the immunologic status of patients are functioning and operative. The number of patients with unusual immunologic diseases who are available to Dr. Good and on whom he already has extensive immunological data is unequaled.

Significance to Biomedical Research and the Program of the Institute: Knowledge of the immunological capability of humans and their response to viral oncogenes and to viral induced tumor antigens is of great importance to the development of effective means of human cancer control. The project under this contract will provide information and materials from carefully selected patients suffering from immunodeficiency diseases, plus research collaboration between the project officer and his staff and one of the nation's outstanding immunological research teams.

Proposed Course: Continuation with expansion to include study of viral transformation of bone marrow cells and study of effects of nuclear transfer in the Lucké renal tumor of frogs.

Date Contract Initiated: May 13, 1971

Current Contract Level: $275,880

CALIFORNIA, UNIVERSITY OF (NIH-NCI-E-71-2173)

Title: Studies on the Structure and Replication of Viruses and Mechanisms of Regulation

Contractor's Project Directors: Dr. Howard K. Schachman
Dr. Peter Duesberg

Project Officer (NCI): Dr. Robert J. Huebner

Objectives: (1) To study the RNA subunits and the replication of RNA tumor viruses. (2) To study mechanisms of cell regulation including transcriptional control by a satellite virus. (3) Electron microscopic studies of RNA viruses.

Major Findings: (1) The validity of the hypothesis that the a subunit of 60-70S RNA may be responsible for the transforming ability of avian tumor viruses was tested further. In collaboration with Dr. Peter Vogt (Contract No. NIH-NCI-E-72-2032), it was shown that several nontransforming avian tumor viruses such as RAV-2, subgroup B and RAV-7, subgroup C lack the a subunit. Using T5, a transforming mutant of RSV which is temperature-sensitive regarding the transformed state of the cell but not with regard to virus growth, it was found that the a subunit was present in T5, regardless of whether it was grown in transformed cells (at the permissive temperature) or in nontransformed cells (nonpermissive temperature). It was concluded that the a subunit is not the result of the transformed state of the cell but may directly or indirectly be involved in transformation, thus providing evidence for viral genes (oncogenes) being specifically responsible for the neoplastic state.

(2) The ratios of a and b subunits in stocks of transforming viruses varied on passage in tissue culture. In all cases the b subunit class increased at the expense of the a. Nontransforming viruses arose spontaneously from a transforming progenitor (Schmidt-Ruppin RSV) on passage in tissue culture. It thus appears that the RNA of RNA tumor viruses exists in subgenomic fragments like the RNA of influenza virus or Reo virus, and that varying RNA subunits may be selected from exchangeable replicating pools in the infected cell.

(3) It was found that the relatively high template activity of 60-70S RSV RNA is lost after heat-dissociation into 30-40S subunits. It was concluded that the partial double-strandedness of 60-70S RSV RNA, which holds the subunits together, is responsible for its high template activity. This model has been tested by attempts to restore the partial double-strandedness of heat-dissociated RSV RNA.

No success has been achieved in reversing the 60-70S → 30-40S conversion of RSV RNA, as yet, but it has been possible to restore the high template activity of RSV RNA after heat-dissociation by adding oligodeoxynucleotides (oligo dT, oligo dC, oligo dG, but not oligo dA).

(4) An RNase-resistant adenylate (A)rich sequence was found in the 60-70S RNA of Rous sarcoma virus and Rauscher murine leukemia virus. The A-rich sequence contains about 10% of the A of the viral RNA. The molecular weight of the A-rich sequence prepared by exhaustive digestion of 60-70S RSV RNA with pancreatic and T1 RNase was estimated by velocity sedimentation and gel electrophoresis to be about 60,000. After heat or formaldehyde dissociation of the 60-70S RSV RNA complex, A-rich sequences remain linked to the major 30-40S RNA subunits. It was concluded that each 30-40S subunit contains as part of the polynucleotide one or two A-rich sequences. (The finding of A-rich sequences has been confirmed by Dr. Maurice Green at St. Louis University [Contract No. PH43-NIH-NCI-E-67-692] and suggests possibilities for specific molecular and biochemical modification of the A-rich sequences. Another contractor, Dr. Tennant at AEC [Contract No. NIH-NCI-E-(FS-13)] found that synthetic poly A added to the media, specifically inhibited Moloney virus replication in cultured mouse cells.)

(5) A selection method for isolating phenotypically normal cells in cultures of transformed cells has been developed. Normal cells have greater adhesiveness to culture dishes. Treatment of mixed cultures with small doses of trypsin and EDTA, therefore, detaches transformed cells selectively leaving clones of revertant normal cells which can be cultured further.

(6) Dr. Calendar's group has been studying the life cycle of satellite phage P4, which depends on temperate coliphage P2 for help in multiplication. P4 can trans-activate helper genes from a repressed P2 prophage, while the normal cell repressor system remains intact. Their data suggest that translational control as well as transcriptional control may be involved in prophage trans-activation. The mechanism of this activation may be relevant to oncogenesis, if carcinogenic viruses and chemicals act by inducing repressed genes present in the host, which is one of the postulates of the viral oncogene hypothesis.

(7) It has been found that the several pieces of RNA comprising the genome of influenza virus (WSN strain) and the RNA of avian sarcoma virus (B77 strain) both terminate at the 3'-end predominantly in uridine.

Significance to Biomedical Research and the Program of the Institute:

Basic research on RNA tumor virus structure and replication, and studies on mechanisms of cell regulation, provide the basis for understanding viral carcinogenesis that may ultimately lead to the control of human cancer. Studies on the a subunit of 60-70S RNA may localize viral genetic information. Studies of the A-rich sequences in tumor virus RNA, provide a handle for biochemical modification of the RNA.

Proposed Course: (1) Further chemical analyses of the a and the b subunits of avian tumor virus strains. It is planned to determine by analysis of the oligonucleotides obtained after RNase T1 digestion, whether the a subunit is different from the other viral RNA subunits. (2) Investigate the dependence of the template activity of 60-70S RSV RNA on its subunit structure by controlled dissociation of the 60-70S RNA and by analysis of the DNA made by the viral DNA polymerase using the dissociated template. (3) Nuclei have been isolated by lyophilization of cells followed by homogenization and centrifugation in non-aqueous solvents. These nuclei have high DNA and RNA polymerase activities, and will be used in cell-free systems to look for virus-specific sequences. (4) Further attempts will be made to isolate satellite phage P4 mutants, to obtain a large collection of mutants defective in trans-activation of helper genes. Purification of RNA polymerase by a sizing technique for analysis of electrophoretic changes and for phosphorylation. The activity of RNA polymerase on P2 templates will be determined. Electrophoretic changes or phosphorylation in ribosomal proteins will also be analyzed. (5) Fibroblasts inoculated with Rous sarcoma virus will, under appropriate conditions, elaborate many virions which remain near the cells, but exterior to the plasma membranes. A technique is being perfected wherein infected cells are grown on films suitable for electron microscopy. Elaborated virions will spread out from the cells and be gently washed of adhering material, negatively stained, and observed in the electron microscope. In this manner it may be possible to observe structural detail in the complete absence of conventional purification steps.

Date Contract Initiated: June 29, 1971

Current Contract Level: $150,000

MASSACHUSETTS INSTITUTE OF TECHNOLOGY (NCI-E-71-2149)

Title: Studies of Leukemia Virus DNA Polymerase.

Contractor's Project Director: Dr. David Baltimore

Project Officers (NCI): Dr. George Todaro
Dr. Roy Kinard

Objectives: To characterize the enzyme, its product, its mechanism of reaction, and formation of viral RNA during infection.

Major Findings: Using polyribionucleotides as templates, complementary primer was necessary to initiate DNA synthesis. Using poly(A) as a template for the DNA polymerase, the amount of poly(dT) synthesis was proportional to the amount of added template. The best primers were oligodeoxyribonucleotides such as oligo(dT) as a primer for poly(A). Polyribonucleotides were in general much better templates than polyribodeoxynucleotides.

The endogenous reaction involves the copying of the 60S-70S RNA found in the virion. The initial reaction product formed when the virion DNA polymerase copies the endogenous viral RNA consists of small pieces of DNA attached to the 60S-70S RNA. The DNA can be released from the bulk RNA by procedures which disrupt hydrogen bonds. The density of the product is not that of a free DNA but that of a covalently-bonded DNA-RNA hybrid. This finding, which was made both with mouse leukemia virus and avian myeloblastosis virus, indicates that the primer for the endogenous reaction is an RNA molecule.

The globin messenger RNA or, more strictly, the 10S RNA from rabbit reticulocytes polyribosomes, was the best template for the DNA polymerase found. Synthesis of DNA amounting to 30-80% of the added template was observed with this RNA. Actinomycin D inhibited the reaction to about 50% indicating that half of the reaction involved copying of RNA and the other half the copying of the complementary DNA into a double-stranded DNA. In order to investigate the nature of the reaction product they studied its size and its ability to hybridize specifically with 10S RNA. They were able to demonstrate that the product was completely complementary to 10S RNA and was not complementary to other RNA's found in reticulocytes and elsewhere. This RNA may be of utility in many aspects of molecular cell biology and a number of experiments have been initiated using it.

Significance to Biomedical Research and the Program of the Institute: The characterization of the enzyme that produces DNA from the tumor viruses genetic material (RNA) has the highest priority in the SVCP. It may provide much more sensitive techniques for finding cancer virus genetic information in human tumors.

Proposed Course: Continuation with slight decrease in budget.

Date Contract Initiated: May 1, 1971

Current Contract Level: $75,000

JEWISH HOSPITAL AND MEDICAL CENTER OF BROOKLYN (NCI-E-72-2034)

Title: Viral Transformation and Chromosome Abnormalities in Human Tumors.

Contractor's Project Director: Dr. Harvey Dosik

Project Officers (NCI): Dr. George Todaro
Dr. Roy Kinard

Objectives: To conduct systematic clinical, epidemiologic and cytogenetic investigations of patients and relatives of patients with chromosome abnormalities, increased risk of malignancy and those on chemotherapy for malignancy, and to supply NCI investigators with cell cultures, serum or other specimens from such patients.

Major Findings: Skin fibroblast cultures, blood cell cultures and cytogenetic analyses have been done on 70 patients and an equal number of controls. These are being studied in collaboration with Dr. Todaro to determine the extent to which genetic and chromosomal factors contribute to cellular susceptibility to transformation by both oncogenic RNA and oncogenic DNA viruses. Neoplastic and normal tissues with chromosome analyses have been supplied to SVCP on request.

Significance to Biomedical Research and the Program of the Institute: These studies are enabling the SVCP to determine, on a broader scale, the relationship between chromosome anomalies (particularly those which involve an excess of genetic material), susceptibility to cellular transformation by oncogenic agents and an increased incidence of malignancy.

Proposed Course: Continue to supply normal and neoplastic tissues from individuals with chromosome abnormalities as requested by NCI for ongoing cancer virus studies within the SVCP.

Date Contract Initiated: October 7, 1970

Current Contract Level: $84,700

PUBLIC HEALTH RESEARCH INSTITUTE OF THE CITY OF NEW YORK, INC. (NCI-E-72-2028)

Title: Study of Cell Surface Alterations Induced by RNA and DNA Viruses.

Contractor's Project Director: Dr. Thomas Benjamin

Project Officers (NCI): Dr. George Todaro
Dr. Roy Kinard

Objectives: To investigate the relationship between cell surface alterations induced by RNA viruses and those induced by DNA viruses using several oncorna viruses and non-transforming mutants of polyoma virus.

Major Findings: Eight cell lines including 3T3, 3T12 and sarcoma virus transformed lines, have been transferred from Dr. Todaro's laboratory successfully and are being checked for possible selection of variants. This contract is new and no other results have been obtained.

Significance to Biomedical Research and the Program of the Institute: The long range goal of the research program of this laboratory is an understanding of how oncogenic viruses overcome cellular growth controls. Ultimately, an understanding of the mechanism of neoplastic transformation by viruses will depend on progress in two areas: (1) the identification and characterization of those viral gene functions which are essential to the transformation process, and (2) the determination of how and where these essential viral genes interact with the cell and with factors which normally operate in regulating cell growth. The proposed contract will allow Dr. Benjamin to continue and extend his impressive work on this problem and will foster collaboration with other NCI and SVCP workers.

Proposed Course: Continuation to achieve the objectives described.

Date Contract Initiated: December 3, 1971

Current Contract Level: $36,800

BAYLOR COLLEGE OF MEDICINE (NCI-E-72-2058)

Title: Development of Suppressor Mutants of 3T3 Mouse Cells.

Contractor's Project Director: Dr. Thomas Caskey

Project Officer (NCI): Dr. George Todaro

Objectives: To develop suppressor mutants of 3T3 mouse cell lines

and use these to investigate genes involved in maintaining transformed state in cell cultures.

Major Findings: None reported. The contract has been in effect too short a time to expect any results.

Significance to Biomedical Research and the Program of the Institute: Understanding of the mechanism of action of tumor viruses will require an understanding of the specific genes of the viruses that are responsible for transforming a normal cell into a tumor cell. For these studies, viral and cellular mutants will be essential. The systems of suppressor mutation that Dr. Caskey proposes to develop have unique advantages. They are simpler, less expensive, and produce "absolute" mutants. The project under this contract will provide extremely valuable reagents for the whole SVCP.

Proposed Course: Continuation to achieve objectives described above.

Date Contract Initiated: January 15, 1972

Current Contract Level: $60,500

UNIVERSITY OF ILLINOIS AT THE MEDICAL CENTER (NCI-72-2031)

Title: Studies on the Molecular Mechanism of Carcinogenesis by Oncogenic Viruses.

Contractor's Project Director: Dr. Giampiero di Mayorca

Project Officer (NCI): Dr. George Todaro

Objectives: Development of a system of mutants of MSV by isolation and characterization of temperature sensitive mutants and of lethal mutants for transformation of mouse, hamster, rat sarcoma viruses; identification of the viral proteins responsible for transformation by polyoma and mouse sarcoma viruses; and studies of the mechanisms and kinetics of transformation in cell cultures.

Major Findings: None reported. This contract has been in effect only a few months; the laboratories are only now becoming really operational.

Significance to Biomedical Research and the Program of the Institute: This project will make available important information regarding the molecular mechanism by which viruses cause tumors. In addition, it will develop the technology necessary for the development of vaccine from human tumor virus, if and when such viruses will be discovered.

Proposed Course: Continuation to achieve objectives described.

Date Contract Initiated: December 9, 1971

Current Contract Level: $220,420

BIONETICS RESEARCH LABORATORIES (NIH-69-2160)

Title: Support Services for the Special Virus Cancer Program.

Contractor's Project Director: Dr. Robert C. Y. Ting

Project Officer (NCI): Dr. George Todaro

Objectives: To provide a laboratory that will collect, process and test specimens from human and animal sources suspected of containing virus associated antigens or antibodies, and to provide other virology, immunology or cell culture services as required.

Major Findings: Services and resources provided in close collaboration with NCI investigators during the past year include: (1) biochemical studies of cell growth regulation with Dr. Todaro; (2) attempts to isolate a human cancer virus with Dr. Bassin; (3) tests for EBV antigens for Dr. Levine; (4) immunological tests of leukemia patients, including studies of twins, for Dr. Levine; (5) CF tests for gs antigens for Dr. Hellman; (6) membrane antigen preparation from human tissue for Dr. Herberman; (7) collection of familial cancer sera and histories for Dr. Fraumeni; (8) tissue and serum bank for Dr. Levine et al; (9) American Burkitt registry and follow-up; and (10) data processing with Dr. Waggoner.

When abortively transformed cells containing SV40 genome were re-infected with SV40, they had a lower rate of transformation than cells without the genome; thus, the presence of SV40 did not confer immunity.

Fetal thymus cells of dogs were cocultivated with irradiated human sarcoma cells. The dog cells showed degeneration and transformation (chromosome analysis now being done).

Rhesus cell cultures infected with Mason-Pfizer virus showed evidence of transformation and caused regressing tumors when subsequently inoculated into newborn rhesus monkeys.

Cellular immunity studies of leukemia patients, using lymphocyte cytotoxicity and cytotoxicity inhibition tests, suggest that cells of such patients possess leukemia-associated antigens and that a widespread antigen system may be operative in human and animal tumors.

Significance to Biomedical Research and the Program of the Institute: This contract laboratory provides an opportunity for a systematic,

large-scale effort to detect viruses and/or viral antigens in human tumor materials (particularly leukemias and sarcomas), using tissue culture, immunological, biochemical and EM techniques. This is a major objective of the SVCP.

Proposed Course: It is proposed that this contract will continue to supply the necessary supportive services required to meet the needs of the SVCP.

Date Contract Initiated: June 27, 1969

Current Contract Level: $800,000

A. PUBLISHED PAPERS

1. Aaronson, S.A.: Chemical induction of focus-forming virus from nonproducer cells transformed by murine sarcoma virus. Proc Natl Acad Sci USA 68: 3069-3072, Dec. 1971.

2. Aaronson, S.A., Bassin, R.H. and Weaver, C.: Comparison of murine sarcoma viruses in nonproducer and SL-transformed cells. J Virol 9: 701-704, April 1972.

3. Aaronson, S.A., Todaro, G.J. and Scolnick, E.M.: Induction of murine C-type viruses from clonal lines of virus-free BALB/3T3 cells. Science 174: 157-159, Oct. 1971.

4. Aaronson, S.A. and Weaver, C.A.: Characterization of murine sarcoma virus (Kirsten) transformation of mouse and human cells. J Gen Virol 13: 245-252, Nov. 1971.

5. Ablashi, D.V., Armstrong, G.R. and Blackham, E.A.: Certain characteristics of herpesvirus saimiri cultured in subhuman primate cell cultures. Am J Vet Res 33: 1689-1694, 1972.

6. Ablashi, D.V., Armstrong, G.R., Heine, U. and Adamson, R.H.: Establishment of a cell culture from an owl monkey tumor induced by herpesvirus saimiri (HSV). Proc Am Assoc Cancer Res 13; Abstr, 494, 1972.

7. Ablashi, D.V., Armstrong, G.R., Heine, U. and Manaker, R.A.: Propagation of herpes virus saimiri in human cells. J Natl Cancer Inst 47: 241-244, July 1971.

8. Ablashi, D.V., Chopra, H.C. and Armstrong, G.R.: A cytomegalovirus isolated from an owl monkey. Lab Anim Sci 22(2): 190-195, April 1972.

9. Ablashi, D.V., Loeb, W.F., Armstrong, G.R., Yang, S.S., Valerio, M.G. and Adamson, R.H.: Oncogenicity of herpesvirus saimiri-induced lymphoma and the DNA polymerases of the lymphoma-derived cell line and herpesvirus saimiri. Proc 3rd Conf Exp Med & Surg in Primates, Lyon, France, June 1972, S. Karger, Basel, Switzerland.

10. Ablashi, D.V., Loeb, W.F., Valerio, M.G., Adamson, R.H., Armstrong, G.R., Bennett, D.G. and Heine, U. Malignant lymphoma with lymphocytic leukemia induced in owl monkeys by herpesvirus saimiri. J Natl Cancer Inst 47(4): 837-855, Oct. 1971.

11. Ablashi, D.V., Turner, W., Armstrong, G.R. and Bass, L.R. Characterization of murine Rauscher leukemia virus propagated in human cells. J Natl Cancer Inst 48: 615-621, March 1972.

12. Ada, G.L. and Hanna, M.G., Jr.: Fate of antigen in vivo: a review. In: Progress in Immunology, Proc 1st Int Cong of Immunology, Washington, D.C., Aug. 1971 Academic Press, New York, 1971, pp 1165-1168.

13. Adam, E., Kaufman, R.H., Levy, A.H., Melnick, J.L. and Rawls, W.E.: Serological study of herpesvirus type 2 infection in invasive cancer of the cervix. Bacteriol Proc: Abstr, 192, 1972.

14. Adam, E., Levy, A.H., Rawls, W.E. and Melnick, J.L.: Seroepidemiologic studies of herpes virus type 2 and carcinoma of the cervix. I. Case-control matching. J Natl Cancer Inst 47(5): 941-951, Nov. 1971.

15. Adam, E., Sharma, S.D., Zeigler, O., Iwamoto, K., Melnick, J.L., Levy, A.H. and Rawls, W.E.: Seroepidemiologic studies of herpesvirus type 2 and carcinoma of the cervix. II. Uganda. J Natl Cancer Inst 48(1): 65-72, Jan. 1972.

16. Adamson, R.H., Ablashi, D.V., Armstrong, G.R. and Ellmore, N.W.: Effect of cytosine arabinoside, adenine arabinoside, tilorone and rifamycin SV on multiplication of herpesvirus saimiri in vitro. Antimicrob Agents Chemother 1: 82-83, Jan. 1972.

17. Ahmed, M., Korol, W., Larson, D., Molnar, H. and Schidlovsky, G.: Transformation of rat mammary cell cultures by R-35 virus isolated from spontaneous rat mammary adenocarcinoma. J Natl Cancer Inst 48(4): 1077-1083, April 1972.

18. Ahmed, M., Larson, D., Molnar, H. and Manousos, M.: Antigens of R-35 virus isolated from spontaneous mammary tumor of a rat. Bacteriol Proc 1972.

19. Ahmed, M., Molnar, H., Slattery, S. and Schidlovsky, G.: Coat and core antigens of M P/M virus isolated from spontaneous mammary carcinoma of a monkey. Proc Am Assoc Cancer Res: 13, 1972.

20. Ahmed, M. and Schidlovsky, G.: Detection of virus-associated antigen on membranes of cells productively infected with Marek's disease herpesvirus. Cancer Res 32: 187-192, Feb. 1972.

21. Ahmed, M., Stafford, M., Cabiness, J.R. and Reeves, W.J.: Cell- and antibody-mediated immune reactions to a cell line established from the bone marrow of a patient with osteosarcoma. Proc Annu Mtg SW Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 1971.

22. Allen, D.W. and Sarma, P.S.: Identification and localization of avian leukosis group-specific antigen within "leukosis-free" chick embryos. Virology 48(3): 624-626, June 1972.

23. Allen, P.T., Georgiades, J., Bowen, J.M., Newton, W.A., Priori, E.S. and Dmochowski, L.: Biochemical characterization of the transforming agent found in cultures derived from human neoplasms. Bacteriol Proc: Abstr 1972.

24. Allen, P.T., Rodgers, R.L., Bowen, J.M. and Dmochowski, L.: Characterization of reverse transcriptase activity of murine sarcoma virus. Bacteriol Proc: Abstr 198, 1972.

25. Ambrose, K.R., Anderson, N.G. and Coggin, J.H., Jr.: Concomitant and sinecomitant immunity to SV40 tumors in cancer. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.).

26. Ambrose, K.R., Anderson, N.G. and Coggin, J.H., Jr.: Cytostatic antibody and SV40 tumor immunity in hamsters. Nature 233: 321, Sept. 1971.

27. Ambrose, K.R., Anderson, N.G. and Coggin, J.H., Jr.: Interruption of SV40 oncogenesis with human fetal antigen. Nature 233: 194, Sept. 1971.

28. Anderson, K.D. and Lilly, J.R.: Allograft survival in rats rejecting cancer. Pediatr Res 6: Abstr 123, 1972.

29. Anderson, K.D. and Lilly, J.R.: Cancer immunotherapy and allograft rejection. Proc Am Pediatr Surg Assoc 3: Abstr 28, 1972.

30. Anderson, N.G.: Screening for cancer. ORNL Review, Spring, 1972.

31. Anderson, N.G. and Coggin, J.H., Jr.: Embryonic antigens in virally transformed cells. Proc Bell Symp, Univ. of Minnesota Med School, Minneapolis, June 1972.

32. Anderson, N.G. and Coggin, J.H., Jr.: Models of Differentiation, retrogression, and cancer. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.).

33. Andersson, B.: Cellular selection in the regulation of antibody affinity during the immune response. In: Cell Interactions, (L.G. Silvestri, ed.) North-Holland Publishing Co., Amsterdam, 1971, pp 100-111.

34. Aoki, T.: Surface antigens of murine leukemia cells and murine leukemia viruses. Transplant Proc III: 1195-1198, 1971.

35. Aoki, T., Geering, G., Beth, E. and Old, L.J.: Suppression of antigens in Burkitt's lymphoma and human melanoma cells grown in selected human sera. In: Recent Advances in Human Tumor Virology and Immunology, (W. Nakahara, D. Nishioka, T. Hirayama and Y. Ito, eds.), Univ Tokyo Press, 1971, pp 425-429.

36. Aoki, T. and Hashimoto, Y.: Human tumor immunology. I.: Chugai-Iyaku 24: 164-174, 1971.

37. Aoki, T. and Hashimoto, Y.: Human tumor immunology. II.: Chugai-Iyaku 24: 223-228, 1971.

38. Aoki, T. and Hashimoto, Y.: Human tumor immunology. III.: Chugai-Iyaku 24: 268-276, 1971.

39. Aoki, T. and Takahashi, T.: Viral and cellular surface antigens of murine leukemia and myelomas: serological analysis by immuno-electron microscopy. J Exp Med 135 (3): 443-457, March 1972.

40. Aoki, T., Wood, H.A., Old, L.J., Boyse, E.A., De Harven, E., Lardis, M.P. and Stockpole, C.W.: Another visual marker of antibody for electron microscopy. Virology 45: 858-862, July 1971.

41. Armstrong, G.R., Ablashi, D.V., Easton, J.M. and Adamson, R.H.: Suppression of the cytopathic effects (CPE) of herpesvirus saimiri (HVS) by cytosine arabinoside (CA) in 1° owl monkey cells. Bacteriol Proc: 246, 1972.

42. Aurelian, L., Strandberg, J.D. and Davis, H.J.: HSV-2 antigens absent from biopsed cervical tumor cells; a model consistent with latency. Proc Soc Exp Biol Med 140(2): 404-408, June 1972.

43. Aurelian, L., Strandberg, J.D., Melendez, L.V. and Johnson, L.A.: Herpesvirus type 2 isolated from cervical tumor cells grown in tissue culture. Science 174: 704-707, Nov. 12, 1971.

44. Axel, R., Schlom, J. and Spiegelman, S.: Evidence for translation of viral-specific RNA in cells of a mouse mammary carcinoma. Proc Nat Acad Sci USA 69(3): 535-538, March 1972.

45. Axel, R., Schlom, J. and Spiegelman, S.: Presence in human breast cancer of RNA homologous to mouse mammary tumor virus RNA. Nature 235(5332): 32-36, Jan. 7, 1972.

46. Bader, A.V. and Steinberg, R.L.: A photographic developing unit for use in autoradiographic electron microscopy. Stain Technol 41(4): 213-214, July 1972.

47. Balcavage, W.X., Ko, M., Baxter-Gabbard, K.L. and Levine, A.S.: Mitochondrial alterations associated with avian reticulendotheliosis virus (strain T) pathogenicity. Fed Proc 31(2) 1972.

48. Ball, F.L. and Harris, W.W.: Predictability of quantitation of small virions by electron microscopy. Proc Soc Exp Biol Med 139(3): 728-733, March 1972.

49. Bansal, S.C., Hargreaves, R. and Sjogren, H.O.: Facilitation of polyoma tumor growth in rats by blocking sera and tumor eluate. Int J Cancer 9: 97-108, Jan. 1972.

50. Bansal, S.C. and Sjogren, H.O.: "Unblocking" serum activity in vitro in the polyoma system may correlate with antitumor effects of antiserum in vivo. Nature 223: 76-77, August 1971.

51. Barker, K.L., Lee, K.L. and Kenney, F.T.: Turnover of tryosine transaminase in cultured hepatoma cells after inhibition of protein synthesis. Biochem Biophys Res Commun 43: 1132-1138, 1971.

52. Bass, L.A. and Turner, W.: A semi-micro XC cell assay technique for murine leukemia virus. Appl Microbiol 23: 200-201, Feb. 1972.

53. Bassin, R.H., Phillips, L.A., Kramer, M.J., Haapala, D.K., Peebles, P.T., Nomura, S. and Fischinger, P.J.: Transformation of mouse 3T3 cells of murine sarcoma virus: release of virus-like particles in the absence of replicating murine leukemia helper virus. Proc Natl Acad Sci USA 68(7) 1520-1524, July 1971.

54. Baxter-Gabbard, K.L., Campbell, W.F., Padgett, F. and Levine, A.S.: Avian reticuloendotheliosis virus (strain T). II. Biochemical and biophysical properties. Avian Dis 15(4): 850-862, Oct.-Dec. 1971.

55. Baxter-Gabbard, K.L. and Levine, A.S.: Avian reticuloendotheliosis virus as an immunogen vs reticuloendotheliosis and Rous sarcoma. Bacteriol Proc: 231, 1972.

56. Baxter-Gabbard, K.L., Peterson, D.A., Levine, A.S., Meyers, P. and Sigel, M.M.: Avian reticuloendotheliosis virus as an immunogen vs reticulendotheliosis and Rous sarcoma. Bacteriol Proc 1972.

57. Beard, D., Lapis, K., Chabot, J.F. and Beard, J.W.: Specificity of renal neoplastic response to avian tumor viruses in the chicken. AMVA Poultry Sect Mtg, New Orleans, La., July 1972.

58. Bekesi, J.G., St. Arneault, G. and Holland, J.F.: Chemotherapy and immunotherapy with neuraminidase-treated murine leukemia. Proc Int Cong of Pharmacology, July 1972.

59. Bekesi, J.G., St. Arneault, G. and Holland, J.F.: Increase of leukemia L1210 immunogenicity by Vibrio cholerae neuraminidase treatment. Cancer Res 31: 2130-2132, 1971.

60. Bekesi, J.G. and Holland, J.F.: The investigation and stimulation of immunity in cancer patients: immunotherapy with Vibrio cholerae neuraminidase treated murine leukemia. Coll CNRS, Paris, France, June 23, 1972.

61. Bekesi, J.G., Walter, L. and Holland, J.F.: Immunogenicity of neuraminidase treated 6C3HED lymphoma in C3HHeJ and C3Hf mice. Proc Am Assoc Cancer Res 13: 1972.

62. Ben-Bassat, H., Inbar, M. and Sachs, L.: Changes in the structural organization of the surface membrane in malignant cell transformation. J Membrane Biol 6: 183-194, Nov. 1971.

63. Bergs, V.V.: Rat C-type virus (BV-1): effect of amniotic fluid, fetal serum and hormones in cell culture. Proc Soc Exp Biol Med 140(1): 102-105, May 1972.

64. Bergs, V.V.: Stimulating effect of estrogen on replication of rat mammary-tumor-derived virus (BV-1) in rat-embryo cell cultures. J Natl Cancer Inst 48(4): Abstr 1244, April 1972.

65. Bishop, D.H.L., Ruprecht, R., Simpson, R.W. and Spiegelman, S.: Deoxyribonucleic acid polymerase of Rous sarcoma virus: reaction conditions and anaylsis of the reaction product nucleic acids. J Virol 8(5): 730-741, Nov. 1971.

66. Biswal, N., McCain, B., and Benyesh-Melnick, M.: The DNA of murine sarcoma-leukemia virus. Virology 45(3): 697-706, Sept. 1971.

67. Blomgren, H.: Studies on the proliferation and immunological competence of mouse thymic cells. Akademisk Avhandling, Tryckeri Balder AB, Stockholm: 1-32, 1972.

68. Blomgren, H. and Andersson, B.: Inhibition of erythroid cell growth in irradiated mice by allogeneic lymphoid cells: a quantitative method for graft-versus-host-reactivity of lymphoid cells. Cell Immunol 3(2): 318-325, Feb. 1972.

69. Blomgren, H. and Svedmyr, E.: In vitro stimulation of mouse thymus cells by PHA and allogeneic cells. Cell Immunol 2(4): 285-299, Aug. 1971.

70. Bluming, A.Z., Ziegler, J.L., Fass, L. and Herberman, R.B.: Delayed cutaneous sensitivity reactions to autologous Burkitt lymphoma protein extracts: results of a prospective two and half year study. Clin Exp Immunol 9: 713, 1971.

71. Bonar, R.A., Ishizaki, R. and Beard, J.W.: Immunoelectrophoretic analysis of avian RNA tumor virus groups specific antigens. J Virol 9: 90-101, Jan. 1972.

72. Boone, C.W. and Blackman, K.: Augmented immunogenicity of tumor cell homogenates infected with influenza virus. Cancer Res 32: 1018-1022, May 1972.

73. Boone, C.W., Brandchaft, P.R., Irving, D.N. and Gilden, R.: Quantitative studies on the binding of syngeneic antibody to the surface antigens of AKR virus-induced rat lymphoma cells. Int J Cancer 9(3): 685-692, May 1972.

74. Boone, C.W., Mantel, N., Caruso, T.D., Jr. and Kazam, E: Quality control studies on fetal bovine serum used in tissue culture. In Vitro 7(3): 174-189, Nov.-Dec. 1972.

75. Boucher, D.W., Melnick, J.L. and Mayor, H.D.: Non-encapsidated infectious DNA of adeno-satellite virus in cell co-infected with herpesvirus. Science 173: 1243-1245, Sept. 24, 1971.

76. Bowen, J.M., Mukerjee, M.D., Scanlon, M.D., Trujillo, J.M. and Dmochowski, L.: Studies on the interaction of SV40 with skin fibroblasts from patients with xeroderma pigmentosum. Proc Annu Mtg SW Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 1971.

77. Bowles, C.A., Kerber, W.T., Rangan, S.R.S., Kwatien, R., Woods, W. and Jensen, E.M. Characterization of a transplantable canine immature mast cell tumor. Cancer Res 32(7): 1434-1441, July 1972.

78. Boyd, V.A. and Butel, J.S.: Recovery of an infectious DNA from SV40-transformed hamster cells. Bacteriol Proc: Abstr, 211, 1972.

79. Breillatt, J.P., Harrell, B.W. and Boling, K.W.: Fabric formation on centrifugal fields: fibrin. Proc Soc Exp Biol Med 138(2): 719-722, Nov. 1971.

80. Bronson, D.L., Graham, B.J., Ludwig, H., Benyesh-Melnick, M. and Biswal, N.: Studies on the relatedness of herpes viruses through DNA-RNA hybridization. Biochim Biophys Acta 259: 24-34, 1972.

81. Buckley, P.M., Kawakami, T.G. and McKain, D.: Incorporation of 3H-uridine into woolly monkey sarcoma virus from mammalian cell cultures. Bacteriol Proc 1972.

82. Buell, D.N. and Ebert, P.S.: Delta-aminolevulinic acid synthetase activity during induced erythroid differentiation in a cloned murine leukemia cell line. In Vitro 7: Abstr, 241, Jan-Feb., 1972.

83. Burger, M.M. and Martin, G.S.: Agglutination of cells transformed by Rous sarcoma virus by wheat germ agglutinin and concanavalin A. Nature (New Biol) 237: 9-12, May 3, 1972.

84. Buss, David H. and Voss, W.R.: Evaluation of four methods for estimating the milk yield of baboons. J Nutr 101(7): 901-910, July 1971.

85. Butel, J.S.: Studies with human papilloma virus modeled after known papovavirus systems. J Natl Cancer Inst 48(2): 285-299, Feb. 1972.

86. Butel, J.S., Richardson, L.S., and Melnick, J.L.: Variation in properties of SV40-transformed simian cell lines detected by superinfection with SV and human adenoviruses. Virology 46(3): 844-855, Dec. 1971.

87. Butel, J.S., Tevethia, S.S. and Melnick, J.L.: Oncogenicity and cell transformation by papovavirus SV40: the role of the viral genome. In: Advances in Cancer Research, Vol. 15, 1972, pp 1-55.

88. Caffier, H. and Green, M.: Adenovirus proteins. III. Cell-free synthesis of adenovirus proteins in cytoplasmic extracts of KB cells. Virology 46(1): 98-105, Oct. 1971.

89. Calvin, M., Joss, H., Hackett, A.J. and Owens, R.B.: The effect of rifampician and two derivatives on cells infected with Moloney sarcoma virus. Proc Natl Acad Sci USA 68: 1441-1443, July 1971.

90. Campbell, W.F., Baxter-Gabbard, K.L. and Levine, A.S.: Avian reticuloendotheliosis virus (strain T). I. Virological characterization. Avian Dis 15(4): 837-849, Oct.-Dec. 1971.

91. Campbell, P.A. and Kind, P.: Bone marrow derived cells as target cells for polynucleotide adjuvants. J Immunol 107: 1419, 1971.

92. Caton, J.E., Willis, D.D. and Anderson, N.G.: Variable-speed drive for the mechanical stage of a microscope used as the optical components in a microdensitometer. Anal Biochem 46(1): 232-238, March 1972.

93. Chan, S.P., Maca, R.D., Levine, P.H. and Ting, R.C.: Immunologic studies of human breast cancer. I. serum reactivity against a lymphoid cell line (Belev) derived from a breast cancer patient as detected by complement-fixation test. J Natl Cancer Inst 47: 511-517, Sept. 1971.

94. Chan, S.P., McCoy, J.L., Levine, P.H. and Ting, R.C.: Immunological studies of human breast carcinoma sera with tissue cultured human Belev (F-230) cells. Bacteriol Proc 1972.

95. Chan, E., Schiopp-Stansly, P.E. and O'Connor, T.E.: Infection and transformation of mammalian cell cultures with feline sarcoma virus. Proc Am Assoc Cancer Res: 13, 1972.

96. Charney, J. and Moore, D.H.: Immunization studies with mammary tumor virus. J Natl Cancer Inst 48(4): 1125-1129, April 1972.

97. Chiba, S., Striker, R.L. and Benyesh-Melnick, M.: Microculture plaque assay for human and simian cytomegaloviruses. Appl Microbiol 23(4): 780-783, April 1972.

98. Chopra, H.C., Hooks, J.J., Walling, M.J. and Gibbs, C.J., Jr.: Comparative study of foamy viruses and monkey tumor derived virus. Proc Cold Spring Harbor Symp, New York, 1971.

99. Chopra, H.C., Hooks, J.J., Walling M.J. and Gibbs, C.J., Jr.: Morphology of simian foamy viruses with particular reference to virus isolated from spontaneous tumor of a rhesus monkey. J Natl Cancer Inst 48(2): 451-463, Feb. 1972.

100. Chopra, H.C., Lloyd, B.J., Ablashi, D.V. and Armstrong, G.R.: Morphologic studies of a cytomegalovirus isolated from an owl monkey. J Natl Cancer Inst 48(5): 1333-1340, May 1972.

101. Chopra, H.C. and Oie, H.K.: Possible etiological role of virus particles detected in rat and monkey mammary carcinomas. J Natl Cancer Inst 48(4): 1059-1065, May 1972.

102. Chopra, H.C., Zelljadt, I., Woodside, N. and Walling, M.J.: Studies on virus particles resembling oncogenic RNA viruses in monkey mammary adenocarcinomas. Cancer 28(6): 1406-1415, Dec. 1971.

103. Cikes, M.: Expression of surface antigens on cultured tumor cells in relation to cell cycle. Transplant Proc 3(3): 1161-1166, Sept. 1971.

104. Cikes, M. and Klein, G.: Effects of inhibitors of protein and nucleic acid synthesis on the expression of H-2 and Moloney leukemia virus-determined cell surface antigens on cultured murine lymphoma cells. J Natl Cancer Inst 48(2): 509-515, Feb. 1972.

105. Cleveland, P.H., Jagarlamoody, S.M., Guy, T.J. and McKhann, C.F.: Antibody mediated inhibition of thymidine uptake in tumor cells. Bacteriol Proc 1972.

106. Cochran, A.J., Klein, E. and Petranyi, G.: Migration of lymph node cells during the primary immune response. Transplantation 12(6): 523-525, 1971.

107. Coggin, J.H., Jr., Ambrose, K.R. and Anderson, N.G. Immunization against tumors with fetal antigens. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn, May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.).

108. Coggin, J.H., Jr., Ambrose, K.R., Bellomy, R. and Anderson, N.G.: Tumor immunity in hamsters immunized with fetal antigens. J Immunol 107(2): 526, Aug. 1971.

109. Courtney, R.J. and Benyesh-Melnick, M.: Fractionation of herpes simplex viral-induced proteins by hydroxylapatite column chromatography. Bacteriol Proc Abstr, 1972.

110. Courtney, R.J., Schaffer, P.A., Benyesh-Melnick, M. and Aron, G.M.: Biochemical defects of temperature-sensitive mutants of herpes simplex virus (HSV). Bacteriol Proc Abstr, 1972.

111. Cross, S.S. and Parker, J.C.: Some antigenic relationships of the murine parvoviruses: minute virus of mice, rat virus, and H-1 virus. Proc Soc Exp Biol Med 139: 105, Jan. 1972.

112. Crouch, N.A. and Rapp, F.: Cell-dependent differences in the production of infectious herpes simplex virus at a supraoptimal temperature. J Virol 9(2): 223-230, Feb. 1972.

113. Crouch, N.A. and Rapp, F.: Differential effect of temperature on the replication of type 1 and type 2 herpes simplex viruses. Bacteriol Proc: 203, 1972.

114. Dalton, A.J.: Further analysis of the detailed structure of type B and C particles. J Natl Cancer Inst 48(4): 1095-1099, April 1972.

115. Dalton, A.J.: Observations on the details of ultrastructure of a series of type C viruses. Cancer Res 32(6): 1351-1353, June 1972.

116. Dalton, A.J. and Stewart, S.E.: Intracysternal A particles and C particles. Science 176: 319, 1972.

117. Davis, M.L., Upton, A.C. and Satterfield, L.C.: Growth and senescence of the bone marrow stem cell pool in RFM/Un mice. Proc Soc Exp Biol Med 137: 1452, 1971.

118. Deeney, A.O'C. and Beaudreau, G.A.: DNA from avian myeloblastosis virus (AMV). Proc Am Chem Soc, Div Biol Chem, Abstr, Sept. 1971.

119. Deeney, A.O'C. and Beaudreau, G.S.: DNA of nucleoids of avian myeloblastosis virus. Proc Pacific Slope Biochem Conf: 46, 1972.

120. Deinhardt, F.: Use of marmosets in biomedical research. In: Medical Primatology, (E.I. Goldsmith & J. Moor-Jankowski, eds.) S. Karger, Basel, 1971, pp 918-925.

121. Deinhardt, F., Wolfe, L., Northrup, R., Marszynska, B., Ogden, J., McDonald, R., Falk, L., Shramek, G., Smith, R. and Deinhardt, J.: Induction of neoplasms by viruses in marmoset monkeys. J Med Primatol 1: 29-50, Jan. 1972.

122. De Schryver, A., Klein, G., Henle, G., Henle, W., Cameron, H.M., Santesson, L. and Clifford, P.: EB-virus associated serology in malignant disease: antibody levels to viral capsid antigens (VCA), membrane antigens (MA) and early antigens (EA) in patients with various neoplastic conditions. Int J Cancer 9: 353-364, 1972.

123. De Thé, G.: Problemes poses par les propietes immunologiques communes au lymphome de Burkitt et au du rhinopharnx. Proc Conf sur Cancer et Immunite, Paris.

124. De Thé, G., Ho, H.C., Greenland, T., Geser, A. and Munoz, N.: Association between a herpes-type virus and nasopharyngeal carcinoma - present status of the studies. In: Recent Advances in Human Tumor Virol and Immunol (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.) Univ of Tokyo Press, 1971, pp 297-308.

125. Diamandopoulos, G.T.: Leukemia, lymphoma, and osteosarcoma induced in the Syrian golden hamster by simian virus 40. Science 176: 173-175, April 1972.

126. Didier-Fichet, M.L. and De Thé, G.: Induction d'une expression virale par le 5-bromodeoxyuridine (BUdR) et le 5-iodoeoxyuridine (IUdR) dans des legnes issues de lymphomes de Burkitt et de cancers du rhinopharynx. CR Acad Sci Ser D (Paris) 274: 2549-2552, 1972.

127. Dierlam, P.J., Anderson, N.G. and Coggin, J.H., Jr.: Immunization against tumors with fetal antigens: detection of immunity by the colony inhibition test and by adoptive transfer. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, eds.).

128. Di Siai, P.J., Rutledge, F.N., Smith, J.P. and Sinkovics, J.G.: Cell-mediated immune reaction to two gynecologic malignant tumors. Cancer 28: 1129-1137, 1971.

129. Dixon, F.J., Tonietti, G., Oldstone, M.B.A., Aoki, T. and McConahey, P.J.: The effect of chronic viral infections on NZ mice. In: Immunopathology, VIth Int Symp (P.A. Miescher, ed.) Grune & Stratton, New York, 1972.

130. Dmochowski, L.: Review of the clinical implications of the virus-autoimmune response. Am J Clin Pathol 56(3): 261-264, Sept. 1971.

131. Dmochowski, L.: Viral diagnosis: the patient and the physician. Am J Clin Pathol 57(6): 733-736, June 1972.

132. Dmochowski, L.: Viruses and breast cancer. Hosp Practice 7(1): 73-81, Jan. 1972.

133. Dmochowski, L.: Viruses and breast cancer. Introductory remarks. Cancer 28(6): 1404-1405, Dec. 1971.

134. Dmochowski, L., Liebelt, R.A. and Sibal, L.: Proceedings of the conference on breast cancer in animals and man. Tex Rep Biol Med 29(3): 349-374, Fall 1971.

135. Docherty, J.J., Martyjarvi, R.A. and Rapp, F.: Mechanism of abortive infection of a hamster cell line by herpes simplex virus type 2. Bacteriol Proc 1972.

136. Docherty, J.J., O'Neill, F.J. and Rapp, F.: Differential susceptibility to herpes simplex viruses of hamster cell lines established after exposure to chemically inactivated herpesvirus. J Gen Virol 13: 377-384, Dec. 1971.

137. Docherty, J.J. and Rapp, F.: Abortive infection of viral transformed hamster cells by herpes simplex virus type 2. Fed Proc 31 : 806, 1972.

138. Doller, E., Duff, R. and Rapp, F.: Resistance to superinfection of hamster cells transformed by herpes simplex virus type 2. Bacteriol Proc: 190, 1972.

139. Duenas, A., Adam, E., Melnick, J.L. and Rawls, W.E.: Herpesvirus type 2 in a prostitute population. Am J Epidemiol 95(5): 483-489, May 1972.

140. Duff, R., Knight, P. and Rapp, F.: Variation in oncogenic and transforming potential of PARA (defective SV40)-adenovirus 7. Virology 47 (3): 849-853, March 1972.

141. Duff, R. and Rapp, F.: Oncogenic transformation of hamster cells after exposure to herpes simplex virus type 2. Nature 233(36): 48-50, Sept. 8, 1971.

142. Duff, R. and Rapp, F.: Properties of five hamster cell lines transformed by herpes simplex virus type 2. Proc Am Assoc Cancer Res 13: 8, May 1972.

143. Duff, R. and Rapp, F.: Properties of hamster embryo fibroblasts transformed in vitro after exposure to ultraviolet-irradiated herpes simplex virus type 2. J Virol 8 (4): 469-477, Oct. 1971.

144. Duran-Reynals, M.L. and Lilly, F.: The role of genetic factors in the combined neoplastic effects of vaccinia virus and methylcholanthrene. Transpl Proc 3: 1243-1246, Sept. 1971.

145. East, J.L., Allen, P.T. and Dmochowski, L.: Properties of the virion RNA and RNA-dependent DNA polymerase of murine sarcoma virus. Bacteriol Proc 1972.

146. East, J.L., Maruyama, K., Georgiades, J., Priori, E.S., Bowen, J.M., and Dmochowski, L.: Preliminary physicochemical studies of RNAs from transformed human cells. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971.

147. Ebert. P.S., Maestri, N.E. and Chirigos, M.A.: Erythropoietic responses of mice to infection with Rauscher leukemia virus. Cancer Res 32: 41-47, Jan. 1972.

148. Eckhart, W.: Polyoma gene functions required for cell transformation. Proc Ciba Foundation Symp on Strategy of the Viral Genome, 267-274, 1971.

149. Einhorn, N.: Effect of local radiotherapy on the level of EBV-associated membrane reactive antibodies in the sera of patients with certain malignant tumors. Cancer 29: 714-723, 1972.

150. Einhorn, N., Henle, G., Henle, W., Klein, G. and Clifford, P.: Effect of local radiotherapy on the antibody levels against EBV-induced early and capsid antigens (EA and VCA) in patients with certain malignant tumors. Int J Cancer 9: 182-192, Jan. 1972.

151. Eskeland, T. and Klein, E.: Isolation of 7S IgM and Kappa chains from the surface membrane of tissue culture cells derived from a Burkitt lymphoma. J Immunol 107(5): 1368-1375, Nov. 1971.

152. Eskeland, T., Klein, E., Inoue, M. and Johansson, B.: Characterization of immunoglobulin structures from the surface of chronic lymphocytic leukemia cells. J Exp Med 134: 265-280, July 1971.

153. Essex, M., Kawakami, T.G. and Kurata, K.: Continuous long-term replication of feline leukemia virus (FeLV) in an established canine cell culture (MDCK). Proc Soc Exp Biol Med 139(1): 259-262, Jan. 1972.

154. Essex, M., Klein, G., Deinhardt, F., Wolfe, L.G., Theilen, G.H. and Pearson, L.D.: Induction of the feline oncornavirus-associated cell membrane antigen in human cells. Proc Am Assoc Cancer Res 13: Abstr 57, 1972.

155. Essex, M., Klein, G., Snyder, S.P., and Harrold, J.B.: Antibody to feline oncornavirus-associated cell membrane antigen in neonatal cats. Int J Cancer 8: 384-390, July 1971.

156. Essex, M., Klein, G., Snyder, S. and Harrold, J.B.: Correlation between humoral antibody and regression of tumors induced by feline sarcoma virus. Nature 223: 195-196, Sept. 1971.

157. Evans, D.L., Barnett, J. and Dmochowski, L.: Antigenic relationship between the herpes-type viruses of infectious bovine rhinotracheitis, Marek's disease and Burkitt's lymphoma. Bacteriol Proc: Abstr, 1972.

158. Evans, D.L., Bowen, J.M., Maruyama, K. and Dmochowski, L.: Antigenic relationship between the herpes-type viruses associated with Marek's disease, infectious bovine rhinotracheitis, and Burkitt's lymphoma. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971.

159. Falk, L., Wolfe, L. and Deinhardt, F.: Herpesvirus saimiri (HVS): incidence of latent infection in squirrel monkeys. Fed Proc 31(2): 806, Abstr 86, April 1972.

160. Falk, L., Wolfe, L. and Deinhardt, F.: Isolation of herpesvirus saimiri from blood of squirrel monkeys (saimiri sciureus). J Natl Cancer Inst 48 (5): 1499-1505, May 1972.

161. Falk, L.A., Wolfe, L.G., Hoekstra, J. and Deinhardt, F.: Demonstration of herpesvirus saimiri-associated antigens in peripheral lymphocytes from infected marmosets during in vitro cultivation. J Natl Cancer Inst 48(2): 523-530, Feb. 1972.

162. Falk, L., Wolfe, L., Marczynska, B. and Deinhardt, F.: Characterization of lymphoid cell lines established from herpesvirus saimiri (HVS)-infected marmosets. Bacteriol Proc 38: Abstr 191, April 1972.

163. Faras, A.J., Taylor, J.M., McDonnell, J., Levinson, W. and Bishop, J.M.: Purification and characterization of theDNA polymerase associated with RSV. Biochemistry 11: 2334-2342, June 1972.

164. Faras, T., Fanshier, L., Garapin, A.C., Levinson, W.E. and Bishop, J.M.: The DNA polymerase of Rous sarcoma virus: studies on the mechanism of double-stranded DNA synthesis. J Virol 7: 539, 1971.

165. Farrelly, J.G., Joseph, D., Roberson, L., Tuominen, F.W., Tennant, R.W. and Kenney, F.T.: Methylated polynucleotides as inhibitors of the DNA polymerase of murine leukemia virus. Proc Am Assoc Cancer Res 13: 89, 1972.

166. Feller, W.F. and Chopra, H.C.: Virus-like particles in human milk. Cancer 28(6): 1425-1430, Dec. 1971.

167. Feller, W.F., Stewart, S.E. and Kantor, J.: Primary tissue culture explants of human breast cancer. J Natl Cancer Inst 48: 1117, April 1972.

168. Fenyo, E.M.: Expression of Moloney leukemia virus controlled cell surface antigen in relation to virus release. Transplant Proc 3(3): 1185-1188, Sept. 1971.

169. Fenyo, E.M., Gruendner, G., Klein, G., Klein, E. and Harris, M.: Surface antigens and release of virus in hybrid cells produced by the fusion of A9 fibroblasts with Moloney lymphoma cells. Exp Cell Res 68: 323-331, Sept. 1971.

170. Fenyo, E.M., Nordenskjold, B.A. and Klein, E.: Membrane immunofluorescence on cultured indicator cells as a measure of virus production by mouse L cells and by two Moloney lymphoma sublines differing in immunosensitivity. Ann NY Acad Sci 177: 121-129, 1971.

171. Ferrer, J.F.: The detection of replicating C-type virus in continuous cell cultures established from leukemic cows: effect of the culture medium. J Natl Cancer Inst 47(3): 613-621, Sept. 1971.

172. Ferrer, J.F., Stock, N.D., Avila, L.: Immunologic studies on a C-type virus of bovine cultures. Bacteriol Proc 1972.

173. Fialkow, P.J., Martin, G.M., Klein, G., Clifford, P. and Singh, S.: Evidence for a clonal origin of head and neck tumors. Int J Cancer 9: 133-142, 1972.

174. Fine, D.L., Landon, J.C. and Kubicek, M.T.: Simian tumor virus: demonstration of cytopathic effects in vitro. Science 174: 420-421, Oct. 1971.

175. Fine, D.L., Pienta, R.J., Fabrizio, D.P.A., Holloway, A.M., Chopra, H.C. and Malan, L.B.: Characteristics of Mason-Pfizer monkey virus-transformed cells. In Vitro 7: 258, Jan.-Feb. 1972.

176. Fine, D.L., Pienta, R.J., Kubicek, M.T., Landon, J.C., Chopra, H.C. and Valerio, M.G.: Recovery of infectious virus from tissues of macaca mulata inoculated with Mason-Pfizer monkey virus transformed cells. Bacteriol Proc 211, 1972.

177. Finkel, S.I. and Lilly, F.: Influence of histoincompatibility between mother and foetus on placental size in mice. Nature 234: 102-103, Nov. 1971.

178. Fischinger, P.J. and Haapala, D.K.: Quantitative interactions of feline leukemia virus and its pseudotype of murine sarcoma virus in cat cells: requirement for DNA synthesis. J Gen Virol 13: 203-214, 1971.

179. Fischinger, P.J. and Moore, C.O.: The formation and nature of foci induced by a modified sarcoma virus in human cells. J Gen Virol 12: 59-63, 1971.

180. Fischinger, P.J., Nomura, S., Peebles, P.T., Haapala, D.K. and Bassin, R.H.: Reverserion of murine sarcoma virus transformed mouse cells: variants without a rescuable sarcoma virus. Science 176: 1033-1035, 1972.

181. Fischinger, P.J., Schafer, W. and Seifert, E.: Detection of some murine leukemia virus antigens in virus particles derived from 3T3 cells transformed only by murine sarcoma virus. Virology 47: 229-235, Jan. 1972.

182. Fowler, A.K., Hellman, A.K. Steinman, H.G. and Quatrale, A.C.: Studies on the blastogenic response of murine lymphocytes. I. Quantitative measurement os stimulation by phytohemagglutinin. Proc Soc Exp Biol Med 138: 345, Oct. 1971.

183. Fox, R.R., Meier, H. and Crary, D.D.: Genetic predisposition to tumors in the rabbit. Naturwissenschaften 58: 457-458, 1971.

184. Frankel, J.W. and Groupe, V.: Interactions between Marek's disease, herpesvirus and avian leukosis virus in tissue culture. Nature (New Biol)234: 125, 1971.

185. Freeman, A.E., Kelloff, G.J., Gilden, R.V., Lane, W.T., Swain, A.P. and Huebner, R.J.: Activation and isolation of hamster specific C-type RNA viruses from tumors induced by cell cultures transformed by chemical carcinogens. Proc Natl Acad Sci USA 68: 2386-2390, Oct. 1971.

186. Friberg, S., Jr., Cochran, A.J. and Golub, S.H.: Concanavalin A inhibits tumor cell migration. Nature (New Biol) 232: 121-122, 1971.

187. Fujinaga, K. and Green, M.: Mechanism of carcinogenesis by RNA tumor viruses. V. The RNA and DNA dependent DNA polymerase activities of feline sarcoma virus. J Gen Virol 12: 85-93, 1971.

188. Fujinaga, K., Green, M., Shimada, K., Tsuei, D., Sekikawa, Y. and Ito, Y.: Viral and cellular gene expression in cells transformed by human adenoviruses. In: Recent Advances in Human Tumor Virology and Immunology, (W. Nakahara, K. Nishioka, T. Hirayama, and Y. Ito, eds.), Univ Tokyo Press, 1971.

189. Gail, M.H.: Does cardiac transplantation prolong life? A reassessment. Ann Int Med 76: 815-817, May 1972.

190. Gail, M.H.: Interpretive study of kidney transplant survival data. Transplantation 21: 194-201, Sept. 1971.

191. Gail, M.H., and Boone, C.W.: Cell-subtrate adhesivity: a determinant of cell motility. Exp Cell Res 70: 33-40, Jan. 1972.

192. Gail, M.H., and Boone, C.W.: Cytochalasin effects on BALB/3T3 fibroblasts: dose dependent, reversible alteration of motility and cytoplasmic cleavage. Exp Cell Res 68: 226-228, Sept. 1971.

193. Gallo, R.C., Sarin, P.S., Allen, P.T., Newton, W.A., Priori, E.S., Bowen, J.M. and Dmochowski, L.: Reverse transcriptase in type C virus particles of human origin. Nature(New Biol) 232(31): 140-142, Aug. 4, 1971.

194. Gallo, R.C., Yang, S.S., Smith, R.G., Herrera, F., Ting, R.C. and Fujioka, S.: Some observations on DNA polymerases of human normal and leukemic cells. Nucleic Acid-Protein Interactions - Nucleic Acid Synthesis in Viral Infection: 353-379.

195. Garapin, A.C., Leong, J., Fanshier, L., Levinson, W.E. and Bishop, J.M.: Identification of virus specific RNA in cells infected with Rous sarcoma virus. Biochem Biophys Res Commun 42: 919, 1971.

196. Gardner, M.B., Officer, J.E., Rongey, R.W., Estes, J.D., Turner, H.C, and Huebner, R.J.: C-type RNA tumor virus genome expression in wild house mice. Nature 232: 617-620, Aug. 1971.

197. Gardner, M.B., Rongey, R.W., Johnson, E.Y., DeJournett, R. and Huebner, R.J.: C-type tumor virus particles in salivary tissue of domestic house cats. J Natl Cancer Inst 47(3): 561-568, Sept. 1971.

198. Gazdar, A.F., Chopra, H.C. and Sarma, P.S.: Properties of a murine sarcoma virus isolated from a tumor arising in a NZW/NZB F1 hybrid mouse. I. Isolation and pathology of tumors induced in rodents. Int J Cancer 9: 219-233, Jan. 1972.

199. Gazdar, A.F., Phillips, L.A., Sarma, P.S., Peebles, P.T. and Chopra, H.C.: Presence of sarcoma genome in a "non-infectious" mammalian virus. Nature (New Biol) 234(46): 69-72, Nov. 1971.

200. Gazdar, A.F., Sarma, P.S. and Bassin, R.H.: Properties of a murine sarcoma virus isolated from a tumor arising in an NZW/NZB F1 hybrid mouse. II. Physical and biological characteristics. Int J Cancer 9: 234-241, Jan. 1972.

201. Gazdar, A.F., Steinberg, A.D., Spahn, G.J. and Baron, S.: Interferon inducers: enhancement of viral oncogenesis in mice and rats. Proc Soc Exp Biol Med 139: April 1972.

202. Gazdar, A.F., Weinstein, A.J., Sims, H.L. and Steinberg, A.D.: Enhancement and suppression of murine sarcoma virus induced tumors by Poly I:Poly C. Proc Soc Exp Biol Med 139: 279-285, Jan. 1972.

203. Gazzolo, L. and De The, G.: Nasopharyngeal carcinoma (NPC). II. Ultrastructure of tumor biopsies and subsequent epithelial growth in vitro. J Natl Cancer Inst 48: 73-86, Dec. 1972.

204. Georgiades, J., Evans, D.L., Bowen, J.M., Priori, E.S. and Dmochowski, L.: Common antigenic components in selected human and animal neoplastic tissue. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p 9.

205. Georgiades, J., Priori, E.S., Allen, P.T., Newton, W.A. and Dmochowski, L.: Rescue of transforming activity from human osteosarcoma cells after co-cultivation with human leukemic bone marrow cells. Proc Annu Mtg Southwest Sec Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p 23.

206. Georgiades, J., Priori, E.S., Hales, R., Allen, P.T., Bowen, J.M. and Dmochowski, L.: A cell transforming agent isolated from cultures derived from human neoplasms. Bacteriol Proc Abstr 7, 1972.

207. Georgiades, J., Priori, E.S., Hales, R.L., Bowen, J.M., Allen, P.T., Newton, W.A. and Dmochowski, L.: Rescue of transforming activity from human osteosarcoma cells after co-cultivation with human leukemic bone marrow cells. Proc Am Assoc Cancer Res 434, April 1972.

208. Gergely, L., Klein, G. and Ernberg, I.: Appearance of EBV-associated antigens in infected Raji cells. Virology 45: 10-21, July 1971.

209. Gergely, L., Klein, G. and Ernberg, I.: Host cell macromolecular synthesis in cells containing EBV induced early antigens, studied by combined immunofluorescence and radiography. Virology 45: 22-29, July 1971.

210. Gilden, R.V., Parks, W.P., Huebner, R.J. and Todaro, G.J.: Murine leukemia virus group-specific antigen in the C-type virus-containing human cell line ESP-1. Nature 233: 102-103, Sept. 1971.

211. Glaser, R., Duff, R. and Rapp, F.: Ultrastructure of hamster cells transformed by ultraviolet irradiated herpes simplex virus type 2. Proc Am Assoc Cancer Res 13c 5, May 1972.

212. Glaser, R. and O'Neill, F.J.: Hybridization of Burkitt-lymphoblastoid cells. Science 176: 1245-1247, June 1972.

213. Glaser, R. and O'Neill, F.J.: Somatic cell hybrids of Burkitt lymphoblastoid cells. Bacteriol Proc, 192, 1972.

214. Goldberg, C., Johnson, T. and Deinhardt, F.: Identification of a serum factor which inhibits cell-mediated tumor immunity in man. J Lab Clin Med 78: Abstr 854-855, 1971.

215. Goldberg, R.J., O'Neill, F.J., Conner, R.P. and Rapp, F.: Mechanism of herpes simplex virus latency in vitro. Bacteriol Proc, 191, 1972.

216. Golstein, P., Svedmyr, E.A.J. and Wigzell, H.: Cells mediating specific in-vitro cytotoxicity. I. Detection of receptor-bearing lymphocytes. J Exp Med 134: 1385-1402, Dec. 1, 1971.

217. Golstein, P., Wigzell, H., Blomgren, H., and Svedmyr, E.A.: Cells mediating specific in-vitro cytotoxicity: II. Probable autonomy of thymus-processed lymphocytes (T cells) for the killing of allogeneic target cells. J Exp Med 135(4): 890-906, Apr. 1972.

218. Goodman, N.C., and Spiegelman, S.: Distinguishing reverse transcriptase of an RNA tumor virus from other known DNA polymerases. Proc Natl Acad Sci USA 68(9): 2203-2206, Sept. 1971.

219. Goodman, W.N., Larkin, C., Chan, E. and Gardner, M.B.: Ataxia-Telangiectasia: Report of a case. Bull LA Neuro Soc 36: 21-31, 1971.

220. Graham, B.J., Ludwig, H., Bronson, D.L., Benyesh-Melnick, M. and Biswal, N.: Physicochemical properties of the DNA of herpes viruses. Biochim Biophys Acta 259: 13-23, 1972.

221. Graham, B.J., Minamishima, Y., Dreesman, G.R., Haines, H.G. and Benyesh-Melnick, M.: Complement-requiring neutralizing antibodies in hyperimmune sera to human cytomegaloviruses. J Immunol 107(6): 1618-1630, Dec. 1971.

222. Green, M.: Molecular basis for the attack on cancer. Proc Natl Acad Sci USA 69(4): 1036-1041, Apr. 1972.

223. Green, M.: Search for adenovirus messenger RNA in cancers of man. In: Oncology, Vol V, 1970, (R.L. Clark, R.W. Cumley, J.E. McCay and M.M. Copeland, eds.), Year Book Med Pub Co., pp 156-165.

224. Green, M.: Transcription of viral genes in cells transformed by DNA and RNA tumor viruses. In: Nucleic Acid-Protein Interactions - Nucleic Acid Synthesis in Viral Infection, Miami Winter Symp 1971, Vol 2, (D.W. Ribbons, J.F. Woessner and J. Schultz, eds.), North-Holland Publishing Co., Amsterdam.

225. Green, M., Bragdon, J. and Rankin, A.: 3-cyclic amine derivatives of rifamycin: strong inhibitors of the DNA polymerase activity of RNA tumor viruses. Proc Natl Acad Sci USA 69: 1294-1298, May 1972.

226. Green, M. and Cartas, M.: The genome of RNA tumor viruses contains polyadenylic acid sequences. Proc Natl Acad Sci USA 69(4): 791-794, Apr. 1972.

227. Green, M. and Hodap, M.: Asymmetric transcription of early adenovirus genes by the Escherichia coli RNA polymerase in vitro. J Molec Biol 64: 305-309, March 1972.

228. Green, M., Rokutanda, M., Fuginaga, K., Rokutanda, H., Gurgo, C., Ray, R.K. and Parsons, J.T.: Molecular and submolecular programming of viral oncogenesis. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, D. Nishioka, T. Hirayama and Y. Ito, eds.) Univ of Tokyo Press, 1971.

229. Grotsky, H.W., Hirshaut, Y., Sorokin, C., Sacher, P., Janowitz, H.D. and Glade, P.R.: Epstein-Barr virus and inflammatory bowel disease. Experimentia 27: 1474, 1971.

230. Grundner, G., Fenyo, E.M., Klein, E.M., Klein, G., Klein, E., Bregula, U. and Harris, H.: Surface antigen expression in malignant sublines derived from hybrid cells of low malignancy. Exp Cell Res 68: 315-322, Sept. 1971.

231. Gunven, P.: EBV-associated antibody titers in Burkitt's lymphoma and other diseases. Symp on Viral Aetiology of Human Cancer, Rome, June 1972.

232. Gunven, P. and Klein, G.: Blocking of direct membrance immunofluorescence in titration of membrane-reactive antibodies associated with Epstein-Barr virus. J Natl Cancer Inst 47(3): 539-548, Sept. 1971.

233. Hackett, A.J., Calvin, M., Owen, R.B. and Joss, U.: Inhibition of MSV viral function by rifampicin derivatives. Medicine 51(3): 175-180, 1972.

234. Haines, H.G., Von Essen, R. and Benyesh-Melnick, M.: Preparation of specific antisera to cytomegaloviruses in goats. Proc Soc Exp Biol Med 138(3): 846-849, Dec. 1971.

235. Hampar, B., Derge, J.G., Martos, L.M. and Walker, J.L.: Persistence of a repressed Epstein-Barr virus genome in Burkitt lymphoma cells made resistant to 5-bromodeoxyuridine. Proc Natl Acad Sci USA 68(12): 3185-3189, Dec. 1971.

236. Hampar, B., Derge, J.G., Martos, L.M. and Walker, J.L.: Synthesis of Epstein-Barr virus after activation of the viral genome in a "virus-negative" human lymphoblastoid cell (Raji) made resistant to 5-bromodeoxyuridine. Proc Natl Acad Sci USA 69(1): 78-82, Jan. 1972.

237. Hampar, B., Gilden, R.V., Kelloff, G., Oroszlan, S. and Simms, D.: Immunofluorescent detection of murine and hamster C-type virus species-specific (gs-1) determinants by monospecific guinea pig sera and inter-species specific (gs-3) determinants by tumor bearing rat sera. Int J Cancer 8(3): 425-431, Nov. 1971.

238. Hamper, B., Hsu, K.C., Martos, L.M. and Walker, J.L.: Serological evidence that a herpes-type virus is the etiological agent of heterophile-positive infectious mononucleosis. Proc Natl Acad Sci USA 68(7): 1407-1411, July 1971.

239. Hampar, B., Martos, L.M. and Walker, J.L.: Epstein-Barr virus in human lymphoblastoid cells: enchancing the percentage of virus-positive cells by cocultivation with African green monkey (vero) cells. J Natl Cancer Inst 47(3): 535-537, Sept. 1971.

240. Hanna, M.G., Jr. (Ed.): Contemporary Topics in Immunology, Vol. 1, Plenum Press, New York, 1971.

241. Hanna, M.G., Jr. and Hunter, R.L.: Localization of antigen and immune complexes in lymphatic tissue with special reference to germinal centers. In: Morphologic and Functional Aspects of Immunity, Vol. 12 (K. Lindahal-Kiessling, G. Alm and M.G. Hanna, eds.), Plenum Press, New York, 1971, pp 257-280.

242. Hanna, M.G., Jr., Nettesheim, P. and Peters, L.C.: Evidence of functional microenvironments in lymphatic tissue response to antigen. Nature (New Biol) 232: 204-206, 1971.

243. Hanna, M.G., Jr., Nettesheim, P. and Snodgrass, M.J.: Decreasing immune competence and development of reticulum cell sarcomas in lymphatic tissue of aged mice. J Natl Cancer Inst 46: 809-824, 1971.

244. Hanna, M.G., Jr. and Peters, L.C.: Requirement for continuous antigenic stimulation in the development and differentiation of antibody-forming cells. Effect of antigen dose. Immunology 20: 707-710, 1971.

245. Hanna, M.G., Jr., Szakal, A.K. and Tennant, R.W.: The interaction of RNA viruses and the immune system: immune capacity and pathogenesis. In: Proc 2nd Int Cong for Virology, Budapest, Hungary, June 1971, (J. Melnick, Ed.), pp 312-314.

246. Hanna, M.G., Jr., Tennant, R.W. and Coggin, J.H., Jr.: Suppressive effect of immunization with mouse fetal antigens on growth of cells infected with leukemia virus and on plasma cell tumors. Proc Natl Acad Sci USA 68: 1748-1752, 1971.

247. Hanna, M.G., Jr., Tennant, R.W., Yuham, J.M. and Clapp, N.K.: Evidence for an immune response to endogenous RNA tumor virus in RFM mice. Proc Am Assoc Cancer Res 13: 59, 1972.

248. Hanna, M.G., Jr., Tennant, R.W., Treber, J.A. and Coggin, J.H., Jr.: Immunization with mouse fetal antigens: suppressive effect on gorwth of leukemia-virus-infected cells and plasma cell tumors. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds) pp 267-270.

249. Harris, N.S., Jagarlamoody, S.M., McKhann, C.F. and Najarian, J.S.: Effect of antiplasma cell serum on humoral immune response. J Immunol 108: 958, 1972.

250. Harris, W.W., Harrell, B.W. and Anderson, N.G.: The specificity of antisera from Burkitt's lymphoma and infectious mononucleosis patients: cross reactions with embryonic antigens. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.)

251. Harter, D.H., Schlom, J. and Spiegelman, S.: Characterization of visna virus nucleic acid. Biochim Biophys Acta 240: 435-441, April 1971.

252. Hatanaka, M., Huebner, R.J. and Gilden, R.V.: Specificity of the DNA product of the C-type virus RNA-dependent DNA polymerase. Proc Natl Acad Sci USA 69: 10-12, Jan. 1972.

253. Hatanaka, M., Kakefuda, T., Gilden, R.V. and Callan, E.A.O.: Cytoplasmic DNA synthesis induced by RNA tumor viruses. Proc Natl Acad Sci USA(8): 1844, Aug. 1971.

254. Hatcher, D.W.: Rapid automated analysis performed in parallel. Clin Chem 17(6): 475-480, 1971.

255. Hatfield, D., Portugal, F.H. and Caicuts, M.: Transfer RNA specificity in mammalian tissues and codon responses of seryl transfer RNA. Cancer Res 31: 697-700, 1971.

256. Hayflick, L.: Biology of the mycoplasmatales. In: Mycoplasma and the L Forms of Bacteria, Gordon and Breach, New York (S. Madoff, ed.) pp 3-25.

257. Heath, C.W., Jr., Rosenstock, J.G., O'Connor, D.M. and Goldenson, R.H.: Time-space clusters in childhood leukemia and lymphoma. XIV Int Cong of Hematol, Abstr, July 1972.

258. Hehlmann, R., Kufe, D. and Spiegelman, S.: RNA in human leukemic cells related to the RNA of a mouse leukemia virus. Proc Natl Acad Sci USA 69(2): 435-439, Feb. 1972.

259. Heine, U., Ablashi, D.V. and Armstrong, G.R.: Morphological studies on herpesvirus saimiri in subhuman and human cell cultures. Cancer Res 31(7): 1019-1029, July 1971.

260. Heine, U. and Hinze, H.C.: Morphological studies on herpesvirus sylvilagus in rabbit kidney cell cultures. Cancer Res 32(6): 1340-1350, June 1972.

261. Hellman, A. and Fowler, A.K.: Hormonal-activated expression of the C-type RNA tumor virus genome. Nature (New Biol) 233(39): 142-144, Sept. 29, 1971.

262. Hellstrom, I. and Hellstrom, K.E.: Cellular immunity to human colonic carcinomas. Dis Colon Rectum 15(2): 100-105, 1972.

263. Hellstrom, I. and Hellstrom, K.E.: Evidence for cell-mediated immunity to human tumor antigens. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.) Univ of Tokyo Press, 1971, pp 563-566.

264. Hellstrom, I. and Hellstrom, K.E.: Some aspects of the immune defense against cancer. II. In vitro studies on human tumors. Cancer 28(5): 1269-1271, Nov. 1971.

265. Hellstrom, I., Hellstrom, K.E. and Sjogren, H.O.: Some recent information on "blocking antibodies" as studied in vitro. Transplant Proc 3: 1221-1227, Sept. 1971.

266. Hellstrom, I., Hellstrom, K.E. and Warner, G.A.: Some factors in tumor-free patients cancelling the blocking of cell-mediated tumor immunity. Int J Cancer 8(2): 185-191, Sept. 1971.

267. Hellstrom, K.E. and Hellstrom, I.: Immunity to neuroblastomas and melanomas. Ann Rev Med 23: 19-38, May 1972.

268. Hellstrom, K.E. and Hellstrom, I.: In vitro studies on immunological enhancement of autochthonous and syngeneic tumors. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.) Univ of Tokyo Press, 1971, pp 563-566.

269. Hellstrom, K.E. and Hellstrom, I.: Some aspects of the cellular and humoral immune response to tumor antigens. Triangle 11(1): 23-28, 1972.

270. Hellstrom, K.E.,and Hellstrom, I.: Some aspects of the immune defense against cancer. I. In vitro studies on animal tumors. Cancer 28(5): 1266-1268, Nov. 1971.

271. Hellstrom, K.E., Hellstrom, I., Sjogren, H.O. and Warner, G.A.: Cell-mediated immunity to human tumor antigens. In: Progress in Immunology (B. Amos, ed.) 1971, pp 939-949.

272. Henderson, B.E., Ziegler, J.L. and Templeton, A.C.: Acute necrotizing encephalitis in a patient with Hodgkin's disease. A case report. East African Med J 48: 592-600.

273. Henle, G. and Henle, W.: Antibodies to EBV-induced early antigens in infectious mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.) Univ of Tokyo Press, 1971.

274. Henle, G., Henle, W. and Klein, G.: Demonstration of two distinct components in the early antigen complex of Epstein-Barr virus infected cells. Int J Cancer 8(1): 272-282, July 1971.

275. Henle, W. and Henle, G.: Evidence for a relation of the Epstein-Barr virus to Burkitt's lymphoma and nasopharyngeal carcinoma. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama, and Y. Ito, eds.) Univ of Tokyo Press, 1971.

276. Herberman, R.B.: Serological analysis of cell surface antigens of murine virus-induced tumors. J Natl Cancer Inst 48(1): 265-271, Jan. 1972.

277. Herberman, R.B. and Aoki, T.: Immune and natural antibodies to syngeneic murine plasma cell tumors. J Exp Med 136(1): 94-111, July 1972.

278. Herberman, R.B. Aoki, T. and Todaro, G.J.: Immune and natural antibodies to syngeneic murine plasma cell tumors. J Exp Med 135(2): 94-111, Feb. 1972.

279. Herberman, R.B., Hollinshead, A. and Alford, T.C.: Skin reactive soluble antigen from intestinal cancer cell membranes and relationship to carcinoembryonic antigens. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.) p 331.

280. Herberman, R.B. and Nam, J.M.: Cytotoxic antibody reactive with cultures of lymphoid cells: occurrence in disease and in normal human sera. J Natl Cancer Inst: 47: 489, 1971.

281. Herberman, R.B., Oren, M.E., Rogentine, G.N., Jr. and Fahey, J.L.: Cytolytic effects of alloantiserum in patients with lymphoproliferative disorder. Cancer 28: 365, 1971.

282. Herberman, R.B., Ting, C.C. and Lavrin, D.: Immune reactions to virus-induced leukemia in animals immunized with fetal tissues. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.) p 259.

283. Hercules, J.I. and Von Kaenel, E.: The inactivation of murine viral antigens with Beta-propiolactone. Lab Anim Sci: 21(4): 497-501, Aug. 1971.

284. Hersh, T., Hollinger, F.B., Goyal, R.K., Grubb, M.N. and Melnick, J.L.: Australia antigen and antibody and Alpha-feto protein in hepatoma patients. Int J Cancer 8: 259-263, July 1971.

285. Hewetson, J.F., Gothoskar, B. and Klein, G.: Radioiodine-labeled antibody test for the detection of membrane antigens associated with Epstein-Barr virus. J Natl Cancer Inst 48(1): 87-94, Jan. 1972.

286. Hieniger, H.J., Chen, H.W., Meier, H., Taylor, B.A. and Commerford, L.S.: Studies on the genetic control of cell proliferation. I. Clearance of DNA-bound radioactivity in 19 inbred strains and hybrid mice. Life Sci 11: 87-96, 1972.

287. Hilgers, J., William, W.C., Myers, B. and Dmochowski, L.: Detection of antigens of the mouse mammary tumor (MTV) and murine leukemia virus (MuLV) in cells of cultures derived from mammary tumors of mice of several strains. Virology 45(2): 470-483, Aug. 1971

288. Hilleman, M.R.: Marek's disease vaccine: its implications in biology and medicine. Avian Dis 16(1): 191-199, April 1972.

289. Hirsch, M.S., Phillips, S.M., Scolnick, C., Black, P.H., Schwartz, R.S. and Carpenter, C.B.: Activation of leukemia viruses by graft versus host and mixed lymphocyte reactions in vitro. Proc Natl Acad Sci USA 69(5): 1069-1072, May 1972.

290. Hirsch, M.S., Proffitt, M.R., Tracy, G.S. and Black, P.H.: Age dependent resistance to polyoma and murine sarcoma viruses in mice. J Immunol 108(3): 649-656, March 1972.

291. Hirumi, H., Burton, G.J. and Maramorosch, K.: Electron microscopy of Friend murine leukemia virus in the mid-gut of experimentally infected mosquitoes. J Virol 8(5): 801-804, Nov. 1971.

292. Hoekstra, J. and Deinhardt, F.: Counter-immunoelectrophoresis: rapid method for detecting group-specific antigen and antibodies associated with oncogenic ribonucleic acid viruses. Appl Microbiol 22(6): 1172-1173, Dec. 1971.

293. Holden, H.T., Sigel, M.M. and Meyers, P.: Investigations of the cell surface antigens induced by Rous sarcoma virus. Fed Proc 31: Abstr, 619, 1972.

294. Holland, J.F.: E pluribus unum: presidential address. Cancer Res 31: 1319-1329, Oct. 1971.

295. Holland, J.F., St. Arneault, G. and Bekesi, J.G.: Combined chemo- and immunotherapy of transplantable and spontaneous murine leukemia. Proc Am Assoc Cancer Res 13: 83, 1972.

296. Hoover, E., McCullough, B. and Griesemer, R.: Intranasal transmission of feline leukemia. J Natl Cancer Inst 48(4): 973-983, April 1972.

297. Horta-Barbosa, L., Hamilton, R., Wittig, B., Fuccillo, D.A., Sever, J.L. and Vernon, M.L.: Subacute schlerosing panencephalitis: isolation of suppressed measles virus from lymph node biopies. Science 173: 840-841, 1971.

298. Hou-Jensen, K., Priori, E.S. and Dmochowski, L.: Studies of ultrastructure of Ewing's sarcoma of bone. Cancer 29(2): 280-283, Feb. 1972.

299. Hsu, H.W.: Transport phenomena in zonal centrifuge rotors. III. Particle sedimentation in gradient solutions. Separation Science 6(5): 699-714, Oct. 1971.

300. Huebner, R.J., Sarma, P.S., Kelloff, G.J., Gilden, R.V., Meier, H., Myers, D.D. and Peters, R.L.: Immunologic tolerance of RNA tumor virus genome expressions. Significance of tolerance and prenatal expressions in embryogenesis and tumorigenesis. Ann NY Acad Sci 181: 246-271, May 1971.

301. Huff, S.D., Kawakami, T., Taylor, N. and Scibienski, E.: RNA dependent DNA polymerase in primate oncogenic RNA viruses. FASEB Mtg, Abstr, 1972.

302. Humbert, J.R., Hathaway, W.E., Robinson, A., Githens, J.H. and Peakman, D.C.: Pre-leukemia in children with a missing bone marrow C chromosome and a myeloproliferative disorder. Brit J Haematol 21(6): 705-716, Dec. 1971.

303. Hussa, R.O. and Pattillo, R.A.: Glycogen turnover studies in human hormone-producing trophoblastic cells in continuous culture. Biochem 11(2): 287-292, Jan. 18, 1972.

304. Inbar, M., Ben-Bassat, H. and Sachs, L.: A specific metabolic activity on the surface membrane in malignant cell transformation. Proc Natl Acad Sci USA 68(11): 2748-2751, Nov. 1971.

305. Inbar, M., Ben-Bassat, H. and Sachs, L.: Location of amino acid and carbohydrate transport sites in the surface membrane of mammalian cells. J Membrane Biol 6: 195-209, Nov. 1971.

306. Inbar, M., Ben-Bassat, H. and Sachs, L.: Membrane changes associated with malignancy. Nature (New Biol) 236(61): 3, March 1, 1972.

307. Ishimoto, A. and Ito, Y.: Studies on the susceptibility of C57BL/6 mice to Rauscher virus. III. Anti-Rauscher leukemia antibody in Rauscher virus-inoculated C57BL/6 mice. Proc Jap Cancer Assoc 30: 47, Oct. 1971.

308. Ishimoto, A., Ito, Y. and Maeda, M.: Studies on the susceptibility of C57BL/6 mice to Rauscher virus. II. Multiplication of Rauscher virus in C57BL/6 cells in vivo and in vitro.

309. Ishizaki, R. and Langlois, A.J., Chabot, J. and Beard, J.W.: A component of strain MC29 avian leukosis virus with the property of defectiveness. J Virol 8(6): 821-827, Dec. 1971.

310. Ito, Y.: Advances in tumor virus research (a review). Farumashia 6: 871-875, 1971.

311. Ito, Y.: Cancer and nucleic acid (a review). Keio Med J 49: 65-82, 1972.

312. Ito, Y.: Human cancer and viruses: EB virus and C-type particles (a review). Metabolism (Tai-Sha) 8: 37-43, 1971.

313. Ito, Y.: Oncogenesis and viruses (a review). Int Med (Tokyo) 28: 609-613, 1971.

314. Ito, Y.: RNA virus and oncogenesis (a review). J Clin Sci (Osaka) 7: 1225-1228, 1971.

315. Jagarlamoody, S.M., Guy, T.J. and McKhann, C.F.: The effect of humoral immunosuppression on tumor induction and transplantation. Proc Reticuloendothelial Soc, Abstr, 1971.

316. Jagarlamoody, S.M., Harris, N.S., Najarian, J.S. and McKhann, C.F.: Effect of antiplasmacyte serum on humoral and cellular immunity. Proc Assoc Acad. Surgeons, Abstr, Nov. 1971.

317. Jagarlamoody, S.M. and McKhann, C.F.: Effect of antiplasma cell and antilymphocyte sera on induction and growth of tumors in mice. Fed Proc 32: 767, 1972.

318. Jagarlamoody, S.M. and McKhann, C.F.: Inhibition of tumor induction and transplantation by heterologous antiplasmacyte serum. Proc Soc of Univ. Surgeons, Feb. 1972.

319. Jagarlamoody, S.M. and McKhann, C.F.: Tumor inhibitory effect of anti-plasma cell serum. Surgery 72: 149, 1972.

320. Jagarlamoody, S.M. and McKhann, C.F.: Tumor inhibitory effect of antiplasmacyte serum in mice. Proc Am Assoc Cancer Res 13, 1972.

321. Jakowski, M., Fredrickson, T.N. and Luginbuhl, R.E.: Humoral immunoglobulin response in experimental infection with cell-free and cell-associated Marek's disease virus. Proc 44th Annu Mtg NE Conf on Avian Diseases, Salisbury, Md., June 1972.

322. Jarue, S.M. and Hackett, A.J.: Morphological and biophysical properties of the Mason-Pfizer monkey virus. J Natl Cancer Inst 48(2): 417-422, Feb. 1972.

323. Jensen, E.M., Buscheck, F.T. and Riccardo, D.: Large-scale production of Burkitt lymphoma cells and EB virus in tissue culture. GANN Mono. 10: 123-133, Fall 1971.

324. Johansen, J., Livingston, D. and Vallee, B.: Chemical modification of carboxypeptidase A crystals. Azo coupling with tyrosine-248. Biochemistry 11: 2584-2589, July 1972.

325. Johansson, B., Klein, G., Henle, W. and Henle, G.: Epstein-Barr virus (EBV)-associated antibody patterns in malignant lymphoma and leukemia. II. Chronic lymphocytic leukemia and lymphocytic lymphoma. Int J Cancer 8(1): 475-486, July 1971.

326. Johnson, F.B., Blacklow, N.R. and Hoggan, M.D.: Immunological reactivity of antisera prepared against the sodium-dodecyl-sulfate-treated structural polypeptides of adenovirus-associated virus. J Virol 9(6): 1017-1026, June 1972.

327. Johnson, F.B., Ozer, H.L. and Hoggan, M.D.: Structural proteins of adenovirus-associated virus type 3. J Virol 8(1): 860-863, July 1971.

328. Johnston, P.B.: Toxonomic features of seven serotypes of simian and ape foamy viruses. Infect and Immun 3(6): 793-799, June 1971.

329. Jones, J.M. and Kind, P.D.: Enhancing effect of bacterial endotoxins on bone marrow cells in the immune response of SRBC. J Immunol 108(5): 1453-1455, May 1972.

330. Kacian, D.L., Spiegelman, S., Bank, S., Terada, M., Metafora, S., Dow, L. and Marks, P.S.: In vitro synthesis of DNA components of human genes for globins. Nature 235(58): 167-169, Feb. 9, 1972.

331. Kacian, D.L., Watson, K.F., Burny, A. and Spiegelman, S.: Purification of the RNA-directed DNA polymerase of avian myeloblastosis virus. Biochim Biophys Acta 246(3): 356-383, Aug. 1971.

332. Kafuko, G.W., Day, N.E., Henderson, B.E., Henle, G., Henle, W., Kirya, G., Munube, R.H., Morrow, M.C., Pike, P.G., Smith, P., Tukei, E. and Williams, H. Epstein-Barr virus antibody levels in children from the West Nile District of Uganda: report of a field study. Lancet 1(7753): 706-709, April 1972.

333. Kalter, S.S., Felsburg, P.J., Heberling, R.L. and Nahmias, A.J.: Experimental herpesvirus hominis type 2 infection in nonhuman primates. Proc Soc Exp Biol Med 139(3): 964-968, March 1972.

334. Kawakami, T.G., Huff, S.D., Buckley, P.M., Dungworth, D.L., Snyder, S.P. and Gilden, R.V.: C-type virus associated with gibbon lymphosarcoma. Nature (New Biol) 235(58): 170-171, Feb. 1972.

335. Kawano, T., Kamakatsu, K., Mori, M., Yoshida, T. and Ito, Y.: Alterations of lactate dehydrogenase, non-specific esterase and glucose-6-phosphate dehydrogenase during Shope papillomatosis. Proc Jap Cancer Assoc 30: 226, Oct. 1971.

336. Kelloff, G.J., Hatanaka, M. and Gilden, R.V.: Assay of C-type virus infectivity by measurement of RNA dependent DNA polymerase activity. Virology 48(1): 266-269, April 1972.

337. Kelloff, G., Huebner, R.J. and Gilden, R.V.: Isolation of helper viruses from preparations of hamster specific sarcoma viruses. J Gen Virol 13: 289-294, Sept. 1971.

338. Kelloff, G.J., Long, C., Huebner, R.J. and Gilden, R.V.: Rapid rescue of the defective M-MSV genome by the use of cell fusion. Virology 46(3): 965-968, Dec. 1971.

339. Kelly, T.J., Jr. and Rose, J.A.: Simian virus 40 integration site in an adenovirus 7-simian virus 40 hybrid DNA molecule. Proc Natl Acad Sci USA 68: 1037-1041, 1971.

340. Kersey, J.H., Gatti, R.A., Good, R.A., Aaronson, S.A. and Todaro, G.J.: Susceptibility of cells from patients with primary immunodeficiency diseases to transformation by simian virus 40. Proc Natl Acad Sci USA 69(4): 980-982, April 1972.

341. Kiessling, A.A., Deeney, A. O'C. and Beaudreau, G.S.: DNA and RNA from avian myeloblastosis virus as template for viral DNA polymerase. FEBS Letters 20 (1): 57-60, Jan. 1972.

342. Killander, D., Klein, E., Johansson, B. and Levin, A.: IgM moietics on malignant lymphoid cells. In: Cell Interactions, (L.G. Silvestri, ed.) North-Holland Publishing Co., Amsterdam, 1971, pp 119-127.

343. Kimura, I.: Progression of pulmonary tumor in mice. I. Histological studies of primary and transplanted pulmonary tumors. Acta Path Jap 21(1): 13-56, 1971.

344. Kimura, I., Miyake, T. and Ito, Y.: Spontaneous tumors in A/Jax, BALB/C, C57BL and Swiss mouse. Proc Jap Cancer Assoc 30: 35, Oct. 1971.

345. Kinard, R.: A program for inoculation of primates with potentially oncogenic viruses. In: Medical Primatology (E.I. Goldsmith and J. Moor-Jankowski, eds.) S. Karger, Basel, 1971, pp 895-902.

346. Kingsbury, E. and Smith, H.S.: Ruthenium red staining of SV40 transformants. Bacteriol Proc 1972.

347. Klein, E.: Viral aetiopathogenesis of tumors. Boll 1st Sieroter, Milan 50(3): 140-151, 1971.

348. Klein, E. and Cochran, A.J.: Immunology and malignant disease. Haematologia 5 (3): 179-203, 1971.

349. Klein, G.: Herpesviruses and oncogenesis. Proc Natl Acad Sci USA 69(4): 1056-1064, April 1972.

350. Klein, G.: Immunological aspects of Burkitt's lymphoma. Adv Immun 14: 187-250, 1971.

351. Klein, G.: Membrane antigen changes in Burkitt lymphoma cells. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.) Univ Tokyo Press, 1971.

352. Klein, G.: Virus-induced tumor-associated antigens. In: Proc CIAB Fdn on Strategy of the Viral Genomes (G.E.W. Wolstenholme and M. O'Connor, eds.), 1971. Churchill Livingstone, London, pp 295-315.

353. Klement, V., Freedman, H., McAllister, R.M., Nelson-Rees, W.A. and Huebner, R.J.: Differences in susceptibility of human cells to mouse sarcoma virus. J Natl Cancer Inst 47(1): 65-73, July 1971.

354. Klement, V., Nicholson, M.O. and Huebner, R.J.: Rescue of the genome of focus forming virus from rat non-reproductive lines by 5'-bromodeoxyuridine. Nature (New Biol) 234: 12-14, Nov. 1971.

355. Klement, V., Rowe, W.P., Hartley, J.W. and Pugh, W.E.: Mixed culture cytopathogenicity: a new test for growth of murine leukemia viruses in tissue culture. In: The Year Book of Cancer, Year Book Medical Publishers, Inc., Chicago, 1971, pp 422-423.

356. Knight, P., Duff, R. and Rapp, F.: Latency of measles virus in hamster embryo fibroblasts. Bacteriol Proc, 239, 1972.

357. Krueger, G.R. and Heine, U.I.: Morphogenesis of two immunologically induced mouse lymphomas. Cancer Res 32(4): 573-582, April 1972.

358. Kufe, D., Hehlmann, R. and Spiegelman, S.: Human sarcomas contain RNA related to the RNA of a mouse leukemia virus. Science 175(4018): 182-185, Jan. 14, 1972.

359. Lai, M.C. and Duesberg, P.H.: An adenylic acid-rich sequence in the RNAs of Rous sarcoma virus and Rauscher mouse leukemia virus. Nature 235(5338): 383-386, Feb. 18, 1972.

360. Landgraf-Leurs, M. and Green, M.: Adenovirus DNA. III. Separation of the complementary strands of adenovirus types 2, 7, and 12 DNA molecules. J Mol Biol 60(1): 185-202, Aug. 28, 1971.

361. Langlois, A.J., Veprek, L., Beard, D., Fritz, R.B., and Beard, J.W.: Isolation of a non-focus-forming agent from strain MC29 avian leukosis virus. Cancer Res 31(7): 1010-1018, July 1971.

362. Larkin, E.P. and Lin, Peck-Sun: Fragility differences and recovery of lymphocytes from the blood of normal and leukemic cattle. Oncology 25(4): 289-296, 1971.

363. Larson, D.L., Ahmed, M., Cravat, A.E. and Liszcak, T.: Transformation activity of R-35 virus isolated from a spontaneous rat mammary tumor. Bacteriol Proc 1972.

364. Lasfargues, E.Y., Coutinho, W.G. and Moore, D.H.: Pitfalls in the isolation of a human breast carcinoma virus in tissue culture. J Natl Cancer Inst 48(4): 1101-1104, April 1972.

365. Lausch, R., Ross, S. and Rapp, F.: Effect of cyclophosphamide on host response to syngeneic tumor transplants. Proc Am Assoc Cancer Res 13, 1972.

366. Lausch, R.N., Ross, S.E. and Rapp, F.: Effect of cyclophosphamide on syngeneic transplantation of PARA-adenovirus-7-transformed tumor cells in hamsters. Int J Cancer 9(3): 659-665, May 15, 1972.

367. Laux, D. and Lausch, R.N.: In vitro assay for anti-tumor activity of cyclophosphamide. Bacteriol Proc, 116, 1972.

368. Lee, K.L. and Kenney, F.T.: Assessment of hormone action in cultured cells. In: In Vitro Methods in Reproductive Cell Biology, Proc 3rd Karolinska Symp, 1971, pp 109-125.

369. Lee, K.L. and Kenney, F.T.: Regulation of tyrosine-alpha-ketoglutarate transaminase in rat liver: regulation of L-leucine in cultured hepatoma cells. J Biol Chem 246: 7595-7601, 1971.

370. Leis, J.P. and Hurwitz, J.: RNA-dependent DNA polymerase activity of RNA tumor viruses. I. Directing influence of DNA in the reaction. J Virol 9(1): 116-129, Jan. 1972.

371. Leis, J.P. and Hurwitz, J.: RNA-dependent DNA polymerase activity of RNA tumor viruses. II. Directing influence of RNA in the reaction. J Virol 9(1): 130-142, Jan. 1972.

372. Leong, J., Garapin, A.C., Jackson, N., Fanshier, L., Levinson, W.E. and Bishop, J.M.: Virus-specific ribonucleic acid (RNA) in cells producing Rous sarcoma virus: detection and characterization. J Virol 9(6): 891-902, July 1972.

373. Leong, J., Levinson, W. and Bishop, J.M.: Synchronization of Rous sarcoma virus production in chick embryo cells. Virology 47(1): 133-141, Jan. 1972.

374. Levin, A.G., Killander, D., Klein, E., Nordenskjold, B.A. and Inoue, M.: Applications of microspectrofluorimetry in quantitation of immunofluorescence on single cells. Ann NY Acad Sci 177: 481-489, 1971.

375. Levine, P.H., Merrill, D.A., Bethlenfalvay, N.C., Dabich, L., Stevens, D.A. and Waggoner, D.E.: A longitudinal comparison of antibodies to Epstein-Barr virus and clinical parameters in chronic lymphocytic leukemia and chronic myelocytic leukemia. Blood 48: 477-479, Oct. 1971.

376. Levinson, W., Varmus, H., Garapin, A.C. and Bishop, J.M.: DNA of Rous sarcoma virus: its nature and significance. Science 175(4017): 76-78, Jan. 7, 1972.

377. Levinson, W., Woodson, B., and Jackson, J.: Inactivation of Rous sarcoma virus upon contact with N-ethyl isatin B-thiosemicarbazone. Nature(New Biol) 232: 116, 1971.

378. Levy, H., Adamson, R., Carbone, P., DeVita, Y., Gazdar, A.F., Rhim, J., Weinstein, A. and Riley, F.: Studies on the antitumor effect of Poly I: Poly C. In: Biological Effects of Polynucleotides, (R. Beers and W. Braun, eds.), Springer-Verlag, New York, 1971, pp 55-65.

379. Levy, J.A. and Rowe, W.P.: Lack of requirement of murine leukemia virus for early steps in infection of mouse embryo cells by murine sarcoma virus. Virology 45(3): 844-847, Sept. 1971.

380. Liebelt, A.G., Liebelt, R.A. and Dmochowski, L.: Cytoplasmic inclusions in primary and transplanted mouse hepatomas -- a genetically determined cellular alteration. J Natl Cancer Inst 47(2): 413-427, Aug. 1971.

381. Lilly, F.: The influence of H-2 type on Gross virus leukemogenesis in mice. Transpl Proc 3: 1239-1241, Sept. 1971.

382. Lilly, F. and Duran-Reynals, M.L.: Combined neoplastic effects of vaccinia virus and 3-methylcholanthrene. II. Genetic factors. J Natl Cancer Inst 48(1): 105-112, Jan. 1972.

383. Lilly, F., Jacoby, J. and Coley, R.: Immunologic unresponsiveness to the H-2.2 antigen. In: Immunogenetics of the H-2 Locus, (A. Lengerova, ed.), S. Karger, Basel, 1971, pp 197-199.

384. Lilly, J.R., Anderson, K.D. and Houck, J.C.: Prolong survival of hepatic allografts after host liver ischemia. Ped Res 6: 120, 1972.

385. Lin, T.M., Yang, C.S., Ho, S.W., Chiou, J.F., Lin, C.H., Yu, S.M., Chen, K.P., Ito, Y., Kawamura, A. and Hirayama, T.: Antibodies to herpes-type virus in nasopharyngeal carcinoma and control group. Cancer 29(3): 603-609, March 1972.

386. Livingston, D.M., Scolnick, E.M., Parks, W.P. and Todaro, G.J.: Affinity chromatography of RNA tumor virus reverse transcriptase on a solid phase immunoadsorbent. Proc Natl Acad Sci USA 69(2): 393-397, Feb. 1972.

387. Loeb, W.F., Valerio, M.G., Ablashi, D.V. and Armstrong, G.R.: Lymphoma induction and virus isolation from an owl monkey inoculated with lymph cells induced by herpesvirus saimiri. Proc Am Vet Med Assoc, July 1972.

388. Lopez, D.M., Meyers, P. and Sigel, M.: Increased thymidine incorporation by peripheral leukocytes from chickens inoculated with Rous sarcoma viruses or Rous-associated viruses following cultivation in the presence of homologous and heterologous viruses. Fed Proc 31(2): Abstr 2281, Mar-April 1972.

389. Lowry, S.P., Bresnick, E. and Rawls, W.E.: Differences in thymidine kinase-inducing ability of herpesvirus types 1 and 2. Virology 46(1): 958-961, Oct. 1971.

390. Lowy, D.R., Rowe, W.P., Teich, N. and Hartley, J.W.: Murine leukemia virus: high-frequency activation in vitro by 5-iododeoxyuridine and 5-bromodeoxyuridine. Science 174(4005): 155-156, Oct. 8, 1971.

391. Ludwig, H., Biswal, N., Bryans, J.T. and McCombs, R.M.: Some properties of the DNA from a new equine herpesvirus. Virology 45(2): 534-537, Aug. 1971.

392. Ludwig, H., Haines, H.G., Biswal, N. and Benyesh-Melnick, M.: The characterization of varicella-zoster virus DNA. J Gen Virol 14: 111-114, 1972.

393. Manning, J.S. and Hackett, A.J.: Morphological and biophysical properties of the Mason-Pfizer monkey virus (M-PMV). J Natl Cancer Inst 48(2): 417-422, Feb. 1972.

394. Manning, J.S., Hackett, A.J. and Darby, N.B., Jr.: Effect of polycations on sensitivity of BALB/3T3 cells to murine leukemia and sarcoma virus infectivity. Appl Microbiol 22(6): 1162-1163, Dec. 1971.

395. Mantyjarvi, R.A.: Growth of simian adenovirus SA7 during arginine starvation. Acta Path Microbiol Scand Sect B 80: 117-122, 1972.

396. Martin, G.S. and Duesberg, P.H.: The a-subunit in the RNA of transforming avian tumor viruses: I. Occurrence in different virus strains. II. Spontaneous loss resulting in nontransforming variants. Virology 47(2): 494-497, Feb. 1972.

397. Maruyama, H.B., Hatanaka, M. and Gilden, R.V.: The 3' terminal nucleosides of the high molecular weight RNA of C-type viruses. Proc Natl Acad Sci USA 68: 1999-2001, Sept. 1971.

398. Maruyama, K., Romero, J.J., Wagner, S.H. and Dmochowski, L.: Retrieval of focus-forming agent from human neoplasms in culture. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p 24.

399. Maruyama, K., Swearingen, G., Dmochowski, L.: A study of antigenic relationship between feline and murine leukemia viruses by immunoelectron microscopy. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p 1.

400 Maruyama, K., Wagner, S.H. and Dmochowski, L.: Tumors induced by feline viral-sarcoma in rats. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p 34.

401. Maruyama, K., Wagner, S.H., Romero, J.J. and Dmochowski, L.: Studies of tumors induced by feline viral sarcoma. Bacteriol Proc, 5, 1972.

402. Mason, M.M., Bogden, A.E., Chopra, H.C., Ilievski, V., Esber, H.J. and Baker, J.R.: History of a rhesus monkey adenocarcinoma containing virus particles resembling oncogenic RNA viruses. J Natl Cancer Inst 48(5): 1323-1331, May 1972.

403. Massey, R., Johnson, T. and Deinhardt, F.: Lymphocyte and antibody tumor cell cytotoxicity measured by a micro 51Cr release assay. Fed Proc 31(2): Abstr 3100, Mar-April 1972.

404. Massicot, J.G., Woods, W.A. and Chirigos, M.A.: Cell line derived from a murine sarcoma virus (Moloney pseudotype)-induced tumor: cultural, antigenic, and virological properties. Appl Microbiol 22(6): 1119-1122, Dec. 1971.

405. Mayyasi, S., Garon, C., Caffarella, V. and Maca, R.: Antigens of human tumor cells reacting with murine virus group-specific antisera. Bacteriol Proc 1972.

406. McAllister, R.M., Green, M. and Gilden, R.V.: Adenoviruses in human cancers. Lancet 1(7755): 831-833, April 15, 1972.

407. McAllister, R.M., Nelson-Rees, W.A., Johnson, E.Y., Rongey, R.W. and Gardner, M.B.: Disseminated rhabomyosarcomas formed in kittens by cultured human rhabdomyosarcoma cells. J Natl Cancer Inst 47(3): 603-611, Sept. 1971.

408. McAllister, R.M., Nicolson, M., Gardner, M.B., Rongey, R.W., Rasheed, S., Sarma, P.S., Huebner, R.J., Hatanaka, M., Oroszlan, S., Gilden, R.V., Kabigting, A. and Vernon, L.: C-type virus released from cultured human rhabdomyosarcoma cells. Nature(New Biol) 235 (53): 3-6, Jan. 1972.

409. McCammon, J.R. and Yohn, D.S.: Application of an indirect paired radioiodine labeled antibody technique to adenovirus 12 tumor serology. J Natl Cancer Inst 47(1): 447-454, July 1971.

410. McCammon, J.R. and Yohn, D.S.: Membrane antigens on adenovirus-12 (Ad-12) infected cells. Bacteriol Proc 1972.

411. McCombs, R.M., Brunschwig, J.P., Minkovic, R., and Benyesh-Melnick, M.: Electron microscopic characterization of a herpes-like virus isolated from tree shrews. Virology 45(3): 816-820, Sept. 1971.

412. McCoy, J.L., Herberman, R.B., Rosenberg, E.B., Levine, P.H. and Alford, T.C.: Cellular lymphocyte cytotoxicity reactivity in human leukemia and tissue culture systems. Proc Conf Cellular Immune Reactions to Human Tumor Assoc Antigens, June 1972.

413. McCoy, J.L., Ting, R.C., Morton, D.L. and Law, L.W.: Immunologic and virologic studies of a non-producer tumor induced by murine sarcoma virus (Harvey). J Natl Cancer Inst 48(2): 383-391, Feb. 1972.

414. McCullough, B.: Interferon response of cats. J Infect Dis 125(2): 174-177, Feb. 1972.

415. McCullough, B., Hoover, G.A. and Hardy, W.D.: Susceptibility of the germ-free cats to Rauscher murine leukemia virus. Am J Vet Res 32: 2077-2079, 1971.

416. McCullough, B., Schaller, J., Shadduck, J.A. and Yohn, D.C.: Induction of malignant melanomas associated with fibrosarcomas in gnotobiotic cats inoculated with Gardner-feline fibrosarcoma virus. J Natl Cancer Inst 48(6): 1893-1896, June 1972.

417. McDonald, R., Wolfe, L. and Deinhardt, F.: Feline fibrosarcoma virus: quantitative focus assay, focus morphology and evidence for a "helper virus". Int J Cancer 9(1): 57-65, Jan. 1972.

418. McKhann, C.F.: Immunobiology of cancer. In: Transplantation (J.S. Najarian and R.L. Simmons, eds.), Lea and Febriger, 1972, pp 297.

419. McKhann, C.F.: What's new in surgery--Tumors. Surg Gynecol Obstet 134: 283, 1972.

420. McKhann, C.F. and Jagarlamoody, S.M.: Evidence for immune reactivity against neoplasms. Transplant Rev 7: 55-77, 1971.

421. McKhann, C.F. and Jagarlamoody, S.M.: In vitro immunization for immunotherapy. 3rd Internat Conf on Lymphatic Tissue and Germinal Centers in Immune Reactions, (K. Lindahl-Kiessling, G. Alm and M.G. Hanna, eds.), Plenum Press, New York, 1971, pp 539-544.

422. McPhedran, P., Heath, C.W.,Jr. and Garcia, J.: Multiple myeloma incidence in metropolitan Atlanta, Georgia: racial and seasonal variations. Blood 39: 866-873, 1972.

423. Meier, H. and Huebner, R.J.: Host-gene control of C-type tumor virus-expression and tumorigenesis: relevance of studies in inbred mice to cancer in man and other species. Proc Natl Acad Sci USA 68(11): 2664-2668, Nov. 1971.

424. Melendez, L.V., Hunt, R.D., King, N.W., Barahona, H.H., Daniel, M.D., Fraser, C.E., and Garcia, F.G.: Herpesvirus ateles, a new lymphoma virus of monkeys. Nature(New Biol) 235(58): 182-184, Feb. 1972.

425. Meyers, P., Sigel, M.M. and Holden, H.T.: Cross protection in-vivo against avian sarcoma virus subgroups A B and C induced by Rous-associated viruses. J Natl Cancer Inst 49: July 1972.

426. Miller, M., Bowen, J.M., Angermann, J., McBride, C.M., Hersh, E. and Dmochowski, L.: Ultrastructural morphology and immunoelectron microscopy of human malignant melanoma cells grown in tissue culture. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Oct. 15-16, 1971, pp 35.

427. Minamishima, Y., Graham, B.J., and Benyesh-Melnick, M.: Neutralizing antibodies to cytomegaloviruses in normal simian and human sera. Infect Immun 4(4): 368-373, Oct. 1971.

428. Mittal, K.K., Mickey, M.R., Terasaki, P.I.: Heterogeneity of HL-A specificities shown by platelet complement fixation. Tissue Antigens 1: 279-285, Nov. 1971.

429. Miyake, T., Kaimura, I. and Ito, Y.: Ascites pulmonary adenocarcinoma with diploid chromosome in A/Jax strain of mice. Proc Japan Cancer Assoc 30: 224, Oct. 1971.

430. Miyake, T., Kimura, I. and Ito, Y.: Development of squamous cell carcinoma in autotransplanted uterus. Prog Med Sci 78: 81-83, 1971.

431. Miyake, T., Kimura, I. and Ito, Y.: A semi-quantitative method for the formation of tumor nodules in rabbit lung: experiments with Vx2 carcinoma. Oncology 25: 481-486, 1971.

432. Moore, D.H., Sarkar, N.H., Kramarsky, B., Lasfargues, E.Y. and Charney, J.: Some aspects of the search for a human mammary tumor virus. Cancer 28: 1415-1424, Dec. 1971.

433. Mukerjee, D. and Bowen, J.M.: Influences of the cell cycle on uptake of SV40 DNA by diploid human cells. Experientia 27: 560, 1971.

434. Mukerjee, D., Trujillo, J.M., Cork, A. and Bowen, J.M.: Genetic susceptibility of human cells to transformation. Proc 4th Int Cong Human Genetics, Paris, France, Sept 1971.

435. Myers, D.D., Meier, H., Huebner, R.J., Vernon, L., and Walker, J.: Cell-free transmission of mouse neuroblastoma. Nature 234(5324): 100, Nov. 12, 1971.

436. Nadkarni, J.S., Svehag, S.E., Nadkarni, J.J. and Klein, G.: Solubilization of IgM-Kappa specific surface material from Burkitt lymphoma cell lines. Immunology 20(4): 667-679, April 1971.

437. Nagata, Y. and Burger, M.M.: Wheat germ agglutinin. J Biol Chem 247(7): 2248-2250, April 1972.

438. Nathan, C.F., Karnovsky, M.L. and David, J.R.: Alterations of macrophage function in MIF-rich supernatants. In: Immunopathology, 6th Int Symp (Meischer, Grune and Stratton, eds.) 1971, p 250.

439. Nelson-Rees, W.A., Hooser, L.E. and Hackett, A.J.: Cells of rhesus monkey origin bearing Mason-Pfizer monkey virus are chronically infected with poliovirus and resist cytolysis. Proc Annu Mtg Tissue Culture Assoc, 1972.

440. Nelson-Rees, W.A., McAllister, R.M. and Gardner, M.B.: Clonal aspects of the C-type virus-releasing cells of cultured human rhabdomyosarcoma line (RD114) in vitro. Nature (New Biol) 236(66): 147-149, April 5, 1972.

441. Nelson-Rees, W.A., Weaver, J. and Riggs, J.L.: Chromosomes of two strains of a feline cell line (FIB) permanently shedding of a C-type virus. Proc Soc Exp Biol Med 139(1): 6-9, Jan. 1972.

442. Nettesheim, P., Hanna, M.G., Jr., Doherty, D.G., Newell, R.F. and Hellman, A.: Effect of calcium chromate dust, influenza virus, and 100R whole-body X-radiation on lung tumor incidence in mice. J Natl Cancer Inst 47(5): 1129-1144, Nov. 1971.

443. Newton, W.A., Allen, P.T., Maruyama, K. and Dmochowski, L.: Reverse transcriptase in transformed cell lines derived from human neoplasms. Proc Am Assoc Cancer Res 13: 430, 1972.

444. Newton, W.A., Allen, P.T., Maruyama, K., Georgiades, J., Bowen, J.M. and Dmochowski, L.: Reverse transcriptase activity in cultures of transformed human cells. Proc Annu Mtg SW Sect Am Assoc Cancer Res, Oct. 1971, p 25.

445. Nilsson, K., Klein, G., Henle, W. and Henle, G.: The establishment of lymphoblastoid lines from adult and fetal human lymphoid tissue and its dependence on EBV. Int J Cancer 8(1): 443-450, July 1971.

446. Nomura, S., Bassin, R.H. and Fischinger, P.J.: Replication of radiation-induced murine leukemia virus in normal and transformed mouse cells. J Virol 9(3): 494-502, March 1972.

447. Nomura, S., Bassin, R.H., Turner, W., Haapala, D.K. and Fischinger, P.J.: Ultraviolet inactivation of Moloney leukemia virus: relative target size required for virus replication and rescue of "defective" murine sarcoma virus. J Gen Virol 14: 213-217, 1972.

448. Nonoyama, M. and Pagano, J.S.: Replication of viral DNA and breakdown of cellular DNA in Epstein-Barr infection. Bacteriol Proc: Abstract, 192, 1972.

449. Nonoyama, M. and Pagano, J.S.: Replication of viral DNA and breakdown of cellular DNA in Epstein-Barr virus infection. J Virol 9(4): 714-716, April 1972.

450. Noronha, F., Post, J.E., Norcross, N.L. and Richard, C.G.: Induction of group-specific interspecies antibody in a cat by immunization with disrupted feline leukemia virus. Nature (New Biol) 235(14): Jan. 1972.

451. Nowinski, R.C., Sarkar, N.H., Old, L.J., Moore, D.H., Scheer, D.I. and Hilgers, J.: Characteristics of the structural components of the mouse mammary tumor virus. II. Viral proteins and antigens. Virology 46(1): 21-37, Oct. 1971.

452. Nutter, R.L. and Rapp, F.: The effect of B-D-arabinofuranosylcytosine on virus production in various cells infected with herpes simplex virus types 1 and 2. Bacteriol Proc: Abstr, 226, 1972.

453. Officer, J.E., Tecson, N. and Fontanilla, E.: Isolation and characterization of competent sarcoma RNA tumor viruses of wild mice. Bacteriol Proc 1972.

454. Ogino, T. and Rapp, F.: Differences in thermal stability of deoxythymidine kinase activity in extracts from cell infected with herpes simplex virus type 1 or type 2. Virology 46(3): 953-955, Dec. 1971.

455. Ogino, T. and Rapp, F.: Effect of ultraviolet irradiation on infectivity and deoxythymidine kinase activity of herpes simplex viruses. Proc Soc Exp Biol Med 139(3): 783-786, March 1972.

456. Oldstone, M.B.A., Aoki, T. and Dixon, F.J.: Activation of spontaneous murine leukemia virus-related antigen by lymphocytic choriomeningitis virus. Science 174: 843-845, 1971.

457. Oldstone, M.B.A., Aoki, T. and Dixon, F.J.: The antibody response of mice to murine leukemia in spontaneous infection: absence of a classical immunologic tolerance. Proc Natl Acad Sci USA 69(1): 134-138, Jan. 1972.

458. Olsen, R.G., McCammon, J.V., Weber, J. and Yohn, D.S.: Cutaneous skin test for delayed hypersensitivity in hamsters to viral-induced tumor antigens. Can J Microbiol 17(8): 1145-1147, July 1971.

459. Olsen, R.G. and Yohn, D.S.: Detection of cat antibodies toward the mammalian oncornavirus interspecies (gs-3) antigen. Bacteriol Proc 1972.

460. O'Neill, F.J., Goldberg, R.J. and Rapp, F.: Herpes simplex virus latency in cultured human cells following treatment with cytosine arabinoside. J Gen Virol 14: 189-197, Feb. 1972.

461. O'Neill, F.J. and Rapp, F.: Premature chromosome condensation in hamster cells treated with cytochalasin B. J Exp Cell Res 70: 226-229, Jan. 1972.

462. Oren, M. and Herberman, R.: Delayed cutaneous hypersensitivity reactions to membrane extracts of human tumor cells. Clin Exp Immunol 9: 45, 1971.

463. Oroszlan, S., Hatanaka, M., Gilden, R.V. and Huebner, R.J.: Specific inhibition of mammalian RNA C-type virus DNA polymerases by rat antisera. J Virol 8(5): 816-818, Nov. 1971.

464. Orr, H.C., Harris, L.E., Jr., Bader, A.V., Kirschstein, R.L. and Probst, P.G.: Cultivation of cells from a fibroma in a rattlesnake, cartalus horridus. J Natl Cancer Inst 48(1): 259-265, Jan. 1972.

465. Ortiz de Landazuri, M. and Herberman, R.B.: Specificity of cellular immune reactivity to virus-induced tumors. Nature (New Biol): 238(79): 18, July 5, 1972.

466. Oshiro, L.S., Riggs, J.L., Taylor, D.O.N., Lennette, E.H. and Huebner, R.J.: Ferritin-labeled antibody studies of feline C-type particles. Cancer Res 31: 1100-1110, Aug. 1971.

467. Osteen, R.T. and Churchill, W.H.: Lymphocyte-macrophage interaction in tumor cell cytotoxicity. Fed Proc 31(2): Abstr, 610, 1972.

468. Otten, J.A. and Tyndall, R.L.: Physiologic and serologic similarities of sera from pregnant and tumor-bearing animals. Proc Am Assoc Cancer Res 13: 37, 1972.

469. Padgett, F., Baxter-Gabbard, K.L., Raitano-Fenton, A. and Levine, A.S.: Avian reticuloendotheliosis virus (strain T). III. Ultrastructure studies. Avian Dis 15(4): 863-873, Oct-Dec. 1971.

470. Panko, W.B. and Kenney, F.T.: Hormonal stimulation of hepatic ornithine decarboxylase. Biochem Biophys Res Commun 43: 346-350, 1971.

471. Paranjpe, M.S. and Boone, C.W.: Delayed hypersensitivity to SV40 tumor cells in BALB/c mice demonstrated by a radioisotopic foot pad assay. J Natl Cancer Inst: 48(2): 563-566, Feb. 1972.

472. Parks, W.P. and Scolnick, E.M.: Radioimmunoassay of mammalian type-C viral proteins - interspecies antigenic reactivities of the major internal polypeptide. Proc Natl Acad Sci USA 69(7): 1766-1770, July 1972.

473. Parks, W.P., Scolnick, E.M., Ross, J., Todaro, G.J. and Aaronson, S.A.: Immunologic relationships of reverse transcriptase from ribonucleic acid tumor viruses. J Virol 9: 110-115, Jan. 1972.

474. Parks, W.P. and Todaro, G.J.: Biologic properties of syncytium-forming "foamy" viruses. Virology 47: 673-683, March 1972.

475. Parsons, J.T. and Green, M.: Biochemical studies on adenovirus multiplication. XVIII. Resolution of early virus-specific RNA species in Ad 2 infected and transformed cells. Virology 45: 154-162, July 1971.

476. Patrascu, I.V. and Calnek, B.W.: In vitro assay of cell-free turkey herpesvirus. Avian Dis 16(2): 397-413, Jan.-Mar. 1972.

477. Pattillo, R.A.: Chemotherapeutic management of gestational trophoblastic tumors. Milwaukee Med Soc Times XLV(1): 14-15, Jan. 1972.

478. Pattillo, R.A.: Hormone synthesis and function in vitro. In: Nutrition and Metabolism of Tissue Culture Cells. (G. Rothblat and V. Cristofalo, eds.), Academic Press, 1972.

479. Pattillo, R.A.: Studies of HCG from choriocarcinoma cell lines and pregnancy urine. Excerpta-Medica 256: 152, June 1972.

480. Pattillo, R.A., Delfs, E., Ehrhart, J.T., Mattingly, R.F., Hussa, R.O. and Rueckert, A.C.F.: Hormone function on trophoblastic tumors. Proc 29th Ann Clin Mtg Hormone Function in Trophoblastic Tumors. Obstet Gynecol 39(4): 632-633, April 1972.

481. Pattillo, R.A., Hussa, R.O. and Garancis, J.C.: Glycogen metabolism in human hormone-producing trophoblastic cells in continuous culture. I. Regulation of glycogen metabolism by glucose. In Vitro 7: 59-67, Sept.-Oct. 1971.

282. Pattillo, R.A., Hussa, R.O., Huang, W.Y., Delfs, E. and Mattingly, R.F.: Estrogen production by trophoblastic tumors in tissue culture. J Clin Endocrinol Metab 34: 59-61, Jan. 1972.

483. Pattillo, R.A., Rodey, G.H. and Terasaki, P.: Surface properties of hormone secreting trophoblastic cells in culture. In Vitro 7(4): 246-247, Jan.-Feb. 1972.

484. Pattillo, R.A. and Rueckert, A.C.F.: Methodology of in vitro propagation of hormonally active human trophoblastic tissue. Proc 11th Mtg Am Soc Cell Biol, Nov. 17-20, 1971, New Orleans, Abstr 428.

485. Pattillo, R.A., Walborg, E.F., Hause, L.L. and Hussa, R.O.: Cell surface antigens and membrane potentials in reproduction, malignancy and organ transplantation. Proc 1st Int Cong Immunol Mtg, Washington, D.C., Aug. 1971, pp 1227-1232.

486. Pattillo, R.A. Walborg, E.F., Hause, L.L. and Hussa, R.O. The human embryonic trophoblast-A tissue transplant: investigations and electrophysiological properties and binding of phytoagglutinins. In: Embryonic and Fetal Antigens in Cancer, Vol. 1, AEC Symp Series, Oak Ridge, Tenn, May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.).

487. Pearson, J.W., Pearson, G.R. and Chirigos, M.A.: Combined chemo-immunostimulation therapy against murine leukemia. Proc Am Assoc Cancer Res: 13, 1972.

488. Pearson, J.W., Pearson, G.R., Gibson, W.T., Chermann, J.C., and Chirigos, M.A.: Combined chemoimmunostimulation therapy against murine leukemia. Cancer Res 32(5): 904-907, May 1972.

489. Peebles, P.T., Bassin, R.H., Haapala, D.K., Phillips, L.A. Nomura, S. and Fischinger, P.J.: Rescue of murine sarcoma virus from a sarcoma-positive leukemia-negative cell line: Requirement for replicating leukemia virus. J Virol 8(4): 690-694, Oct. 1971.

490. Peebles, P.T., Haapala, D.K. and Gazdar, A.F.: Deficiency of viral ribonucleic acid-dependent deoxyribonucleic-acid polymerase in non-infectious virus-like particles released from murine sarcoma virus-transformed hamster cells. J Virol 9(3): 488-493, March 1972.

491. Peterson, D.A., Baxter-Gabbard, K.L. and Levine, A.S.: Avian reticuleondotheliosis virus (Strain T): V. DNA polymerase. Virology 47(1): 251-254, Jan. 1972.

492. Peterson, D.A. and Levine, A.S.: Avian reticuloendotheliosis virus (Strain T) IV. Infectivity and transmissibility in day-old cockerels. Avian Dis 15(4): 874-883, Oct.-Dec. 1971.

493. Pienta, R.J., Fine, D.L., Hurt, T., Smith, C.K., Landon, J.C. and Chopra, H.C.: In vitro transformation of rhesus foreskin cells by Mason-Pfizer monkey virus (M-PMV). J Natl Cancer Inst 48(4): 914-918, April 1972.

494. Pienta, R.J., Hurt, T., Smith, C., Fine, D.L. and Landon, J.C.: Transformation of rhesus cells by M-PMV. Proc Am Assoc Cancer Res 13: 25, March 1972.

495. Pierce, J.C. Cobb, G.W. and Hume, D.M.: Relevance of HL-A antigens to acute humoral rejection of multiple renal allotransplants. N Engl J Med 285: 142-146, July 15, 1971.

496. Pincus, T.: Immunochemical conditions affecting the measurement of DNA antibodies using ammonium sulfate precipitation. Arthritis Rheum 14: 623-630, 1971.

497. Pincus, T., Hughs, G.R.V., Pincus, D., Tina, L.U. and Bellanti, J.A.: Antibodies to DNA in childhood systemic lupus erythematosus. J Pediatr 78: 981-984, 1971.

498. Pollack, S., Heppner, G., Brawn, R.J. and Nelson, K.: Specific killing of tumor cells in vitro in the presence of normal lymphoid cells and sera from hosts immune to the tumor antigens. Int J Cancer 9(2): 316-323, March 15, 1972.

499. Price, P.J. and Cserepfalvi, M.: Pulp viability and the homotransplantation of frozen teeth. J Dent Res 51: 39-43, 1972.

500. Price, P.J., Suk, W.A., Spahn, G.J. and Freeman, A.E.: Transformation of Fischer rat embryo cells by the combined action of murine leukemia virus and (-)-trans-Delta 9-tetrahydrocannabinol. Proc Soc Exp Biol Med 140(2): 454-456, June 1972.

501. Priori, E.S., Anderson, D.E., Williams, W.C. and Dmochowski, L.: Immunological studies on human breast carcinoma and mouse mammary tumors. J Natl Cancer Inst 48(4): 1131-1135, April 1972.

502. Priori, E.S., Dmochowski, L., Myers, B. and Wilbur, J.R.: Constant production of type C virus particles in a continuous tissue culture derived from pleural effusion cells of a lymphoma patient. Nature(New Biol) 233(28): 61-62, July 14, 1971.

503. Priori, E.S., Dmochowski, L., Myers, B. and Wilbur, J.R.: Continuous type C virus production in a tissue culture of human origin (Burkitt lymphoma). Proc 29th Annu Mtg Electron Microscopy Soc Am, Boston, Mass., Aug. 9-13, 1971.

504. Priori, E.S., Seman, G., Dmochowski, L., Gallager, H.S. and Anderson, D.E.: Immunofluorescence studies on sera of patients with breast carcinoma. Proc 2nd Natl Conf on Breast Cancer, Cancer 28(6): 1462-1471, Dec. 1971.

505. Priori, E.S., Trapani, R., Veronelli, J., Dial, E., Dmochowski, L. and Wilbur, J.R.: Association of ESP-1 culture to donor family. Proc Annu Mtg Southwest Sect Am Cancer Res, Galveston, Texas, Oct. 15-16, 1971, pp 25.

506. Quintrell, N., Fanshier, L., Evans, B., Levinson, W.E. and Bishop, J.M.: The DNA polymerase(s) of a Rous sarcoma virus: Effects of virion-associated endonuclease on the enzymatic product. J Virol 8: 17, 1971.

507. Rabin, H.: Assay and pathogenesis of oncogenic viruses in nonhuman primates. Lab Anim Sci 21(6): 1032-1049, Dec. 1971.

508. Rabin, H. and Cooper, R.W.: Tumor production in squirrel monkeys by Rous sarcoma virus. Lab Anim Sci 21(5): 705-711, Oct. 1971.

509. Rabin, H., Griesemer, R., Espana, C., Theilen, G.H. and Aldrich, C.: Studies on spontaneous lymphosarcomas of rhesus monkeys. In Vitro 7: 257-258, Jan.-Feb. 1972.

510. Rabstein, L.S., Gazdar, A.F., Chopra, H.C. and Abelson, H.T.: Early morphological changes associated with infection by a non-thymic lymphatic tumor virus. J Natl Cancer Inst 46: 481-491, 1971.

511. Randerath, K., Rosenthal, L.J. and Zamecnik, P.C.: Base composition differences between avian myeloblastosis virus transfer RNA and transfer RNA isolated from normal and neoplastic host cells. Proc Natl Acad Sci USA 68: 3233-3237, Dec. 1971.

512. Rangan, S.R.S., Calvert, R.C. and Vitols, K.J.: Fibrillar bundles in canine lymphomas. An ultrastructural study. J Ultrastruct Res 36: 425-426, Oct. 1971.

513. Rangan, S.R.S., Moyer, P., Cheong, M.P. and Jensen, E.M.: Detection and assay of feline leukemia virus (FeLV) by a mixed culture cytopathogenicity method. Virology 47(1): 247-251, Jan. 1972.

514. Rangan, S.R.S., Wong, M.C., Ueberhorst, P. and Ablashi, D.V.: Mixed culture cytopathogenicity induced by virus preparations derived from cultures infected by simian sarcoma virus. J Natl Cancer Inst 48(2): 571-577, Feb. 1972.

515. Rapp, F. and Crouch, N.: The control of nonvirion antigens induced by papovaviruses. Transplant Proc 3(3): 1175-1178, Sept. 1971.

516. Rauscher, F.J.: Major opportunities for determination of etiologies and prevention of cancer in man. In: Recent Advances in Human Tumor Virology and Immunology (W. Nakahara, K. Nishioka, T. Hirayama, and Y. Ito, eds.), Univ Tokyo Press, 1971.

517. Rehacek, J., Dolan, T., Thompson, K., Fischer, R.G., Rehacek, Z. and Johnson, H.: Cultivation of oncogenic viruses in mosquito cells in vitro. Current Topics in Microbiology 55(7): 14-20, 1971.

518. Rein, A. and Smith, H.S.: Partial immunity of SV40 cryptic transformants to retransformation by SV40. Proc Annu Mtg Tissue Culture Assoc, 1972.

519. Rhim, J.S., Cho, H.C., Huebner, R.J., Gordon, R.J., Bryan, W.R. and Gardner, M.B.: In vitro transformation induced by extracts of city smog in mouse cells infected with AKR leukemia virus. Fed Proc 31(2): Abstr 3331, Mar.-Apr. 1972.

520. Rhim, J.S., Cho, H.Y., Joglekar, M.H. and Huebner, R.J.: Comparison of the transforming effect of benzo(a)pyrene in mammalian cell lines in vitro. J Natl Cancer Inst 48: 949-959, April 1972.

521. Rhim, J.S., Creasy, B. and Huebner, R.J.: Production of altered cell foci by 3-methylocholanthrene in mouse cells infected with AKR leukemia virus. Proc Natl Acad Sci USA 68: 2212-2216, Sept. 1971.

522. Rhim, J.S., Demoise, C.F., Duh, F.G. and Cho, H.Y.: Transformation of guinea pig embryo cells by a murine sarcoma virus. Virology 48: 841-843, June 1972.

523. Rhim, J.S., Greenawalt, C., Takemoto, K.K. and Huebner, R.J.: Increased transformation efficiency of simian virus 40 in rat embryo cells infected with Rauscher leukemia virus. Nature 230: 81-83, 1971.

524. Rhim, J.S., Lane, W.T., and Huebner, R.J.: Amantadine hydrochloride: Inhibitory effect on murine sarcoma virus infection in cell culture. Proc Soc Exp Biol Med 139(4): 1258-1260, April 1972.

525. Rhim, J.S., Lengel, C.R., Cho, H.Y., Takemoto, K.K., Turner, H.C., Huebner, R.J. and Gilden, R.V.: Expression of a new complement-fixing antigen reactive with murine sarcoma virus rat antiserum in rat cells transformed by a polyoma virus. Nature 235: 188-190, Feb. 1972.

526. Rhim, J.S., Lengel, C.R., Takemoto, K.K. and Huebner, R.J.: Accelerated transformation by polyoma virus in rat embryo cells infected with Rauscher leukemia virus. Proc Soc Exp Biol Med 138(1): 308-311, Oct. 1971.

527. Rhim, J.S., Vass, W., Cho, H.Y. and Huebner, R.J.: Malignant transformation induced by 7, 12-dimethylbenz(a)antracene in rat embryo cells infected with Rauscher leukemia virus. Int J Cancer 7(1): 65-74, 1971.

528. Rhim, J.S., Vass, W., Huebner, R.J., Sarma, P.S. and Nelson-Rees, W.A.: In vitro transformation of feline embryo cells by a chemical carcinogen. Proc Am Assoc Cancer Res 13: Abstr 230, March 1972.

529. Rhim, J.S., Vernon, M.L., Huebner, R.J., Turner, H.C., Lane, W.T. and Gilden, R.V.: Spontaneous transformation of rat cells after long-term in vitro cultivation and the "switch-on" of a new complement-fixing antigen. Proc Soc Exp Biol Med 140(2): 414-419, June 1972.

530. Rice, J.M., Turner, W., Chirigos, M.A. and Spahn, G.: Dose responsiveness and variation among inbred strains of mice in the production of interferon after treatment with Poly I:Poly C - polylysine complexes. Appl Microbiol 22(3): 380-386, Sept. 1971.

531. Richter, C.B., Estes, P.C. and Tennant, R.W.: Spontaneous stem cell leukemia in young Sprague-Dawley rats. Lab Invest 26: 419-428, 1972.

532. Robb, J.A., Smith, H.S. and Scher, C.D.: Genetic analysis of simian virus 40 III. Characterization of a temperature sensitive mutant blocked at an early stage of productive infection in monkey cells. J Virol 9(6): 956-968, June 1972.

533. Robb, J.A., Smith, H.S., Scher, C.D.: Inhibited transformation on 3T3 cells by a temperature sensitive early SV40 mutant. Bacteriol Proc 1972.

534. Rongey, R.W., Hlavackova, A.L., Officer, J.E. and Gardner, M.B.: Electron microscopic detection of type B and C RNA tumor viruses in normal breast tissue of pregnant wild mice. Bacteriol Proc 1972.

535. Rosenberg, E.B. and Herberman, R.B.: Serum factors in renal carcinoma. Lancet 2: 1153, 1971.

536. Rosenberg, E.B., Herberman, R.B., Levine, P.H., Halterman, R., McCoy, J.L. and Wunderlich, J.R.: Lymphocyte cytotoxicity reactions to leukemia-associated antigens in identical twins. Int J Cancer 9(3): 648-658, May 15, 1972.

537. Ross, J., Aviv, H., Scolnick, E. and Leder, P.: In vitro synthesis of DNA complementary to purified rabbit globin mRNA. Proc Natl Acad Sci USA 69: 264-268, Jan. 1972.

538. Rowe, W.P.: The kinetics of rescue of the murine sarcoma virus genome from a nonproducer line of transformed mouse cells. Virology 46(2): 360-374, Nov. 1971.

539. Rowe, W.P.: The problem of murine virus contamination of a mouse-grown vaccine. In: Immunization for Japanese Encephalitis. (W. McD. Hammon, M. Kitaoka and W.G. Downs, eds.), Tokyo, Igaku Shoin Ltd., 1971, pp 169-171.

540. Rowe, W.P., Hartley, J.W., Lander, M.R., Pugh, W.E. and Teich, N.: Noninfectious AKR mouse embryo cell lines in which each cell has the capacity to be activated to produce infectious murine leukemia virus. Virology 46(3): 864-874, Dec. 1971.

541. Rowe, W.P., Lowy, D.R., Teich, N. and Hartley, J.W.: Some implications of the activation of murine leukemia virus by halogenated pyrimidines. Proc Natl Acad Sci USA 69(4): 1033-1035, April 1972.

542. Rowe, W.P. and Pincus, T.: Quantitative studies of naturally occurring murine leukemia virus infection of AKR mice. J Exp Med 135(2): 429-436, Feb. 1972.

543. Roy-Burman, P., Pal, B.K. and Gardner, M.B.: Inhibitor of the DNA-dependent DNA polymerase of some RNA tumor viruses in feline sera. Nature(New Biol) 237(71): 45-47, May 10, 1972.

544. Rubin, D.J.: Highlights: Sixth Annual Joint Working Conference of the Special Virus Cancer Program. J Natl Cancer Inst 48(5): 1547-1551, May 1972.

545. Sarma, P.S., Gazdar, A.F., Turner, H.C. and Kunchorn, P.D.: Gazdar strain of murine sarcoma virus. Biologic and antigenic interaction with the heterologous hamster host. Proc Soc Exp Biol Med 140: 928-933, 1972.

546. Sarma, P.S., Gilden, R.V. and Huebner, R.J.: A complement-fixation test for the detection of viral antigens and infective virus of feline leukemia and sarcoma. J Am Vet Med Assoc 158: 1055-1060, 1971.

547. Sarma, P.S., Gilden, R.V. and Huebner, R.J.: Complement-fixation test for feline leukemia and sarcoma viruses (the COCAL test). Virology 44: 137-145, 1971.

548. Sarma, P.S., Huebner, R.J., Gilden, R.V., Baskar, J.F. and Gardner, M.B.: In vitro isolation and propagation of the GA strain of the feline sarcoma virus. Proc Soc Exp Biol Med 137: 1333-1336, Sept. 1971.

549. Sarma, P.S. and Log, T.: Viral interference in feline leukemia-sarcoma complex. Virology 44: 352-358, 1971.

550. Sarma, P.S., Log, T. and Theilen, G.: St-feline sarcoma virus propagation and cell transformation in vitro. Proc Soc Exp Biol Med 137: 1444-1448, Sept. 1971.

551. Sarma, P.S., Neubauer, R.H. and Rabstein, L.S.: Murine sarcoma and leukemia viral infection of mice: Effect of long-term treatment with Poly I:Poly C. Proc Soc Exp Biol Med 137: 469-472, 1971.

552. Schafer, W., Fischinger, P.J., Lange, J. and Pister, L.: Properties of mouse leukemia viruses. I. Characterization of various antisera and serological identification of viral components. Virology 47: 197-209, Jan. 1972.

553. Schafer, W., Lange, J., Fischinger, P.J., Frank, H., Bolognesi, D.P. and Pister, L.: Properties of mouse leukemia viruses. II. Isolation of viral components. Virology 47: 210-228, Jan. 1972.

554. Schaffer, P.A., Courtney, R.J., McCombs, R.M. and Benyesh-Melnick, M.: A temperature-sensitive mutant of herpes simplex virus defective in glycoprotein synthesis. Virology 47(2): 356-368, Nov. 1971.

555. Schaffer, P.A., Lewis, R.T. and Benyesh-Melnick, M.: Recombination between temperature-sensitive mutants of herpes virus type 1. Bacteriol Proc, Abstr 203, 1972.

556. Schaller, J.P., Milo, G.E. and Yohn, D.C.: Hormonal enhancement and inhibition of adenovirus transformation. Proc Am Assoc Cancer Res 13: 1972.

557. Schaller, J.P. and Yohn, D.S.: Isolation and transformation capacity of defective adenovirus. Bacteriol Proc 1972.

558. Scher, C.D. and Nelson-Rees, W.: The direct isolation and characterization of "flat" SV40 transformed cells. Nature(New Biol) 233: 263-265, Oct. 1971.

559. Scher, C.D. and Todaro, G.J.: Selective growth of human neoplastic cells in medium lacking serum growth factor. Exp Cell Res 68: 479-481, Oct. 1971.

560. Schidlovsky, G., Ahmed, M., Slattery, S. and Lowry, G.: Electron microscopy of cell transformation by R-35 rat virus and comparative morphology with other oncogenic viruses. J Natl Cancer Inst 48(4): 1067-1075, April 1972.

561. Schidlovsky, G., Harewood, K. and Cummings, B.: Morphology of internal viral components. Proc Am Assoc Cancer Res 13: 1972.

562. Schlom, J., Harter, D.H., Burny, A. and Spiegelman, S.: DNA polymerase activities in virions of visna virus, a causative agent of a "slow" neurological disease. Proc Natl Acad Sci USA 68: 182-186, 1971.

563. Schlom, J. and Spiegelman, S.: DNA polymerase activities and nucleic acid components of virions isolated from a spontaneous mammary carcinoma from a rhesus monkey. Proc Natl Acad Sci USA 68(7): 1613-1617, July 1971.

564. Schlom, J. and Spiegelman, S.: Simultaneous detection of reverse transcriptase and high molecular weight RNA unique to oncogenic RNA viruses. Science 174: 840-843, Nov. 19, 1971.

565. Schlom, J., Spiegelman, S. and Moore, D.H.: Detection of high-molecular weight RNA in particles from human milk. Science 175: 542-544, Feb. 4, 1972.

566. Schlom, J., Spiegelman, S. and Moore, D.H.: Reverse transcriptase and high molecular weight RNA in particles from mouse and human milk. J Natl Cancer Inst 48: 1197-1203, April 1972.

567. Schwartz, D.B., Zbar, B., Gibson, W.T. and Chirigos, M.A.: Inhibition of murine sarcoma virus oncogenesis with living BCG. Int J Cancer 8: 320-325, Sept. 1971.

568. Scolnick, E.M., Parks, W.P., Todaro, G.J. and Aaronson, S.A.: Primate C-type virus reverse transcriptases: immunological properties. Nature(New Biol) 235: 35-40, Jan. 1972.

569. Scott, J.F. and Kuhns, V.L.: Ribonucleic acid from animal tissue by use of chaotropic agents. Ann Biochem 47: 471-480, June 1972.

570. Sekikawa, K., Shimada, K., Ito, Y. and Fujinaga, K.: Virus-specific RNA and cell RNA in adenovirus type 2 transformed rat embryo cells. Proc Jap Cancer Assoc 30: Oct. 1971.

571. Sela, B., Lis, H., Sharon, N. and Sachs, L.: Quantitation of N-acetyl-D-galactosamine-like sites on the surface membrane of normal and transformed mammalian cells. Biochim Biophys Acta 249: 564-568, Dec. 1971.

572. Seman, G., Gallager, H.S. and Dmochowski, L.: Microtubular structures in mitochondria of human breast tumor cells. Proc Annu Mtg SW Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 1971, p. 19.

573. Seman, G., Gallager, H.S. and Dmochowski, L.: Structures suggesting the presence of paramyxoviruses and of small DNA viruses in specimens of human breast cancer tissue. Tex Rep Biol Med 29(3): 429-430, Fall 1971.

574. Seman, G., Gallager, H.S., Lukeman, J.M. and Dmochowski, L: Studies on the presence of particles resembling RNA virus particles in human breast tumors, pleural effusions, their tissue cultures and milk. Cancer 28(6): 1431-1442, Dec. 1971.

575. Shantz, G. and Lausch, R.: Differential susceptibility of transformed hamster cells to cytotoxicity by Forssman antibody. Fed Proc 31(2): 805, March-April, 1972.

576. Shigematsu, T., Dmochowski, L. and Williams, W: Studies on mouse mammary tumor virus (MTV) and mouse leukemia virus (MuLV) by immunoelectron microscopy. Cancer Res: 2085-2097, Dec. 1971.

577. Shigematsu, T., Priori, E.S., Dmochowski, L. and Wilbur, J.R.: Immunoelectron microscopic studies of type C virus particles in ESP-1 and HEK-1-HRLV cell lines. Nature 234(5329): 412-414, Dec. 17, 1971.

578. Shigematsu, T., Priori, E.S., Dmochowski, L. and Wilbur, J.R.: Immunoelectron microscopy of type C virus particles produced in a cell line derived from pleural effusion of a lymphoma patient. Proc 29th Annu Mtg. Electron Microscopy Soc Amer, Boston, Mass., Aug. 9-13, 1971, pp.374-375.

579. Shigematsu, T., Priori, E.S., Hales, R.L. and Dmochowski, L.: Studies of the acid mucopolysaccharide-coat on ESP-1 virus envelopes. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p. 27.

580. Shigematsu, T., Williams, W.C. and Dmochowski, L.: Immunoelectron microscopy studies on mouse mammary tumor (MTV) and mouse leukemia virus (MuLV). Proc Ann Mtg. Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971, p. 16.

581. Sibal, L.R. and Moloney, J.B.: Recent topics on type C RNA virus oncogenesis. In: Recent Advances in Human Tumor Virology and Immunology. Proc 1st Int Symp Princess Takamatsu Cancer Res, Tokyo, Japan, Nov. 24, 1970. (W. Nakahara, K. Nishioka, T. Hirayama and Y. Ito, eds.), Univ Tokyo Press, 1971.

582. Sibal, L.R. and Rubin, D.J.: Antigens of murine mammary tumor virus: applications to human breast cancer. J Natl Cancer Inst 48: 1177-1180, April 1972.

583. Sibinovic, S., Valerio, D.A., Landon, J.C. and Leiseca, S.: Maintenance of juvenile simians for oncogenic studies. In: Medical Primatology 1970 (E. Goldsmith and J. Moor-Jankowski, eds.), S. Karger, New York, pp. 912-917, 1971.

584. Sigel, M.M., Myers, P. and Holden, H.T.: Immunity to Rous sarcoma virus elicited by homologous and heterologous avian leukosis viruses. Proc Am Assoc Cancer Res 13: abstr., 66, 1972.

585. Silberstein, H., McAuslan, B.R. and August, J.T.: Protein kinase and phosphate acceptor proteins of animal viruses. Fed Proc 31(2): 407, March-April, 1972.

586. Silvestre, D., Kourilsky, F.M., Klein, G., Yata, Y., Neauport-Sautes, C. and Levy, J.P.: Relationship between the EBV-associated membrane antigen on Burkitt lymphoma cells and the viral envelope, demonstrated by immunoferritin labeling. Int J Cancer 8: 222-233, July 1971.

587. Simmons, R.L., Rios, A., Lundgren, G., Ray, P.K., McKhann, C.F. and Haywood, G.R.: Immunospecific regression of methylcholanthrene fibrosarcoma using neuraminidase. Surgery 70: 38-46, July 1971.

588. Singh, S.B., McMillan, V.L., Melnick, J.L. and Tevethia, S.S.: Functional characterization of hamster lymphocytes stimulated with concanavalin. Bacteriol Proc: Abstr., 189, 1972.

589. Singh, D.V., Meites, J., Halmi, L., Kortright, K.H. and Brennan, M.J.: Suppression of pituitary prolactin level and transplanted mammary tumor growth in mice by ergocornine. Proc Am Assoc Cancer Res 13: 8, 1972.

590. Singh, S.B., Smith, J.W., Rawls, W.E. and Tevethia, S.S.: Demonstration of cytotoxic antibodies in rabbits bearing tumors induced by Shope fibroma virus. Infect Immun 5(3): 352-358, March 1972.

591. Singh, S.B. and Tevethia, S.S.: In vitro stimulation of hamster lymphocytes with concavalin A. Infect Immun 5(3): 339-345, March 1972.

592. Sinkovics, J.G., Ahmed, N., Cabiness, J.R. and Reeves, W.J.: Serum factors specifically antagonistic to or synergistic with cytotoxic lymphocytes in patients with neoplastic disease. Proc Am Assoc Cancer Res 13, Abstr. 436, 1972.

593. Sinkovics, J.G., Cabiness, J.R., DiSaia, P. and Shullenberger, C.C.: A test for the detection of cell-mediated immunity to human tumors in vitro. 14th Int Cong of Hematology, Abstr., 1972.

594. Sinkovics, J.G., Cabiness, J.R. and Shullenberger, C.C.: Monitoring in vitro of immune reactions to solid tumors. The interrelationships of the immune response and cancer. Frontiers in Radiation Therapy and Oncology 7: 141-154, 1972.

595. Sinkovics, J.G., Gyorkey, F., Cabiness, J.R. and Keil, D.: Effect of mycoplasma contamination of target cells on the in vitro monitoring of cell- and antibody-mediated immune reactions of patients to cultured tumor cells. Bacteriol Proc Abstr, 1972.

596. Sinkovics, J.G., Reeves, W.J. and Cabiness, J.R: Cell-and antibody-mediated immune reactions of patients to cultured cells of breast carcinoma. J Natl Cancer Inst 48: 1145-1149, 1972.

597. Sinkovics, J.G., Sullivan, M.P. and Wilbur, J.R.: Disappearance of blocking serum factors in patients receiving chemotherapy for disseminated rhabdomyosarcoma. Proc 8th Annu Scientific Mtg Am Soc of Clin Oncology, Abstr 57.

598. Sjogren, H.O. and Bansal, S.D.: Antigens in virally induced tumors. In: Progress in Immunology (B. Amos, Ed.) 1971, pp 921-938.

599. Sjogren, H.O., Hellstrom, I., Bansal, S.C., Warner, G.A. and Hellstrom, K.E.: Elution of "blocking factors" from human tumors capable of abrogating tumor cell destruction by specifically immune lymphocytes. Int J Cancer 9: 274-283, March 1972.

600. Skurzak, H.M., Klein, E., Yoshida, T.O. and Lamon, E.W.: Synergistic or antagonistic effect of different antibody concentrations on in vitro lymphocyte cytotoxicity in the Moloney sarcoma virus system. J Exp Med 135(5): 997-1002, May 1972.

601. Smith, H.S., Gelb, L.D. and Martin, M.A.: Detection and quantitation of simian virus 40 genetic material in abortively transformed BALB/3T3 clones. Proc Natl Acad Sci USA 69:. 152-156, Jan. 1972.

602. Smith, H.S., Kingsbury, E., Hiller, A.J. and Dorey, C.R.: Cell surface properties and the expression of SV40 virus transformation. Bacteriol Proc Abstr, 1972.

603. Smith, H., Scher, C. and Todaro, G.J.: Induction of cell division in medium lacking serum growth factor by SV40. Virology 44: 359-370, May 1971.

604. Smith, J.W., Adam, E. and Rawls, W.E.: Use of the chromium release test to detect antibodies to herpesvirus. Bacteriol Proc Abstr, 246, 1972.

605. Smith, J.W., Lowry, S.P, Melnick, J.L. and Rawls, W.E.: Antibodies to surface antigens of herpesvirus type 1- and type 2-infected cells among women with cervical cancer and control women. Infect Immun 5(3): 305-310, March 1972.

606. Smith, R.G., Whang-Peng, J., Gallo, R.C., Levine, P. and Ting, R.C.: Selective toxicity of rifamycin derivatives for leukaemic human leukocytes. Nature (New Biol) 236: 166-171, April 1972.

607. Smith, R.G., Whang-Peng, J., Levine, P. and Ting, R.C.: Selective toxicity of rifamycin derivatives for leukaemic human leucocytes. Nature (New Biol) 236: 166-171, April 1972.

608. Smoler, D., Molineux, I. and Baltimore, D.: Direction of polymerization by the avian myeloblastosis virus DNA polymerase. J Biol Chem 246: 7697-7700, 1971.

609. Snodgrass, M.J., Lowrey, D. and Hanna, M.G., Jr.: Changes induced by lactic dehydrogenase virus in thymus and thymus-dependent areas of lymphatic tissue. J Immunol 108: 877-892, 1972.

610. Snyder, S.P.: Spontaneous feline fibrosarcomas: transmissibility and ultrastructure of associated virus-like particles. J Natl Cancer Inst 47(5): 1079-1085, Nov. 1971.

611. Sohier, R. and De Thé, G.: Evolution of complement-fixing antibody titers with the development of Burkitt's lymphoma. Int J Cancer 9: 524-528, 1972.

612. Sohier, R. and De Thé, G.: Fixation du complement avec un antigene soluble: differences d'activite importanes entre les serums de lymphome de Burkitt, de cancer du rhinopharynx et de monoucleose infectieuse. CR Acad Sci (Paris) 273: 121-124, July 1971.

613. Soule, H. and Maloney, T.: Granulocytopoiesis and virulent virus porduction in long-term culture. Proc Am Assoc Cancer Res 13: 65, 1972.

614. Spahn, G.J., Chirigos, M.A., Peters, R.L. and Woods, W.A.: Inhibition of C-type RNA virus expression by streptonigrin. In: Proc 23rd Annu Mtg Tissue Culture Assoc, June 1972, Abstr.

615. Spiegelman, S.: DNA and the RNA viruses. Proc Royal Soc London, Series B 177: 87-108, 1971.

616. Spiegelman, S., Axel, R. and Schlom, J.: Viral-related RNA in human and mouse mammary tumors. J Natl Cancer Inst 48: 1205-1211, April 1972.

617. Spiegelman, S. and Schlom, J.: Reverse transcriptase in oncogenic RNA viruses. In: Virus-cell Interactions and Viral Antimetabolites (D. Shugar, ed.) Academic Press, London, 1972, pp 115-133.

618. Spiegelman, S., Watson, K.F. and Kacian, D.L.: Synthesis of DNA complements of natural RNAs: a general approach.. Proc Natl Acad Sci USA 68(11): 2843-2845, Nov. 1971.

619. Stanbridge, E., Perkins, F.T. and Hayflick, L. Modification of amino-acid concentrations induced by mycoplasmas in cell culture medium. Nature (New Biol) 232: 242-244, July 1971.

620. Steck, T.L., Fairbanks, G. and Wallach, D.F.H.: Disposition of the major proteins in the isolated erythrocyte membrane. Proteolytic dissection. Biochemistry 10 (13): 2617-2624, 1971.

621. Steiner, S., Melnick, J.L. and Tevethia, S.S.: Polar lipids of SV40 hamster cell lines differing in immunosensitivity. Bacteriol Proc: Abstr, 216, 1972.

622. Steinman, H.G., Fowler, A.K. and Hellman, A.: Studies on the blastogenic response of murine lymphocytes. II. The effects of serumstimulant-cell interactions on phytohemagglutinin-induced stimulation. Proc Soc Exp Biol Med 140: 48-53, May 1972.

623. Stephens, R., O'Brien, E., Garon, C., Lowry, G. and Mayyasi, S.: Activation studies with human embryonic kidney cells chronically infected with mouse leukemia virus (Rauscher). Bacteriol Proc 1972.

624. Stephenson, J.R. and Aaronson, S.A.: Antigenic properties of murine sarcoma virus transformed BALB/3T3 nonproducer cells. J Exp Med 135: 503-515, March 1972.

625. Stephenson, J.R. and Aaronson, S.A.: Genetic factors influencing C-type RNA virus induction. J Exp Med 136: 175-184, July 1972.

626. Stephenson, J.R. and Aaronson, S.A.: Murine sarcoma and leukemia viruses: genetic differences determined by RNA-DNA hybridization. Virology 46: 480-484, Nov. 1971.

627. Stephenson, J.R., Axelrad, A.A. and McLeod, D.L.: Erythroid nature of the response to Friend leukemia virus infection in mice. J Natl Cancer Inst 48: 531-539, Feb. 1972.

628. Stephenson, J.R., Axelrad, A.A., McLeod, D.L. and Shreeve, M.M.: Induction of colonies of hemoglobin-synthesizing cells by erythropoietin in vitro. Proc Natl Acad Sci USA 68: 1542-1546, July 1971.

629. Stephenson, J.R., Reynolds, R.K. and Aaronson, S.A.: Isolation of murine leukemia virus conditional lethal mutants. Virology 48: 749-756, April 1972.

630. Stephenson, J.R., Scolnick, E.M. and Aaronson, S.A.: Genetic stability of the sarcoma viruses in murine and avian sarcoma virus transformed nonproducer cells. Int J Cancer 9: 577-583, May 1972.

631. Stephenson, M.L., Wirthlin, L.R.S., Scott, J.F. and Zamecnik, P.: The 3'-terminal nucleosides of the high molecular weight RNA of avian myeloblastosis virus. Proc Natl Acad Sci USA 69: 1176-1180, May 1972.

632. Stevens, D.A., Easton, J.M., Levine, P.H., Waggoner, D.E., Manaker, R.A. and Schidlovsky, G.: Antilymphocyte serum and lymphoid cell-virus carrier culture: cell kinetics, morphology, EB virus replication, interferon. Cell Immunol 3(4): 629-643, April 1972.

633. Stevens, D.A. and Pry, T.W.: EB-virus antibodies in post-transfusion mononucleosis and cardipulmonary bypass. J Med Microbiol 4: 13-18, 1971.

634. Stewart, S.E., Kasnic, G. and Draycott, C.: Characterization of viruses activated in human tumors by a modified 5-IUDR technique. In: Gustav Stern Symp on Perspectives in Virology, Vol. 8, Academic Press, 1972.

635. Stewart, S.E., Kasnic, G., Draycott, C. and Ben, T.: Activation of viruses in human tumors by 5-iododeoxyuridine and dimethyl sulfoxide. Science 175: 198, Jan. 14, 1972.

636. Stewart, S.E., Kasnic, G., Draycott, C., Feller, W., Golden, A., Mitchell, E. and Ben, T.: Activation in vitro, by 5-iododeoxyuridine, of a latent virus resembling C-type virus in a human sarcoma cell line. J Natl Cancer Inst 48: 273-277, Jan. 1972.

637. Stjernsward, J. and Levin, A.: Delayed hypersensitivity-induced regression of human neoplasms. Cancer 28: 638-640, Sept. 1971.

638. Stock, N.D. and Ferrer, J.F.: Replicating C-type virus in phytohemagglutinin-treated buffy-coat cultures of bovine origin. J Natl Cancer Inst 48: 985-996, April 1972.

639. Strand, M. and August, J.T.: Protein kinase and phosphate acceptor proteins in Rauscher murine leukaemia virus. Nature (New Biol) 233: 137-140, Sept. 29, 1971.

640. Svedmyr, E.A.J., Demissie, A., Klein, G., Gergely, L. and Clifford, P.: Complexity of antigen-antibody systems associated with Epstein-Barr virus. Ann NY Acad Sci 177: 241-249, June 21, 1971.

641. Swearingen, G., Maruyama, K. and Dmochowski, L.: A study on antigenic relationship between feline and murine leukemia viruses by immunoelectron microscopy. Proc Annu Mtg SW Sect Am Assoc Cancer Res, Galvestion, Texas, Oct. 1971.

642. Takasugi, M.: An improved fluorochromatic cytotoxic test. Transplantation 12: 148, 1971.

643. Takasugi, M., Henderson, B.E. and Terasaki, P.E.: HL-A antigen frequencies in cancer. Proc Am Assoc Cancer Res 13, 1972.

644. Takasugi, M. and Klein, E.: The role of blocking antibodies in immunological enhancement. Immunology 21: 675-684, 1971.

645. Talal, N., Steinberg, A.D. and Gazdar, A.F.: Specific immunosuppression, polyinosinic.polycytidylic acid and viruses in New Zealand mice. Fed Proc 30: 1842-1845, Nov.-Dec. 1971.

646. Talal, N., Steinberg, A., Jacobs, M., Chused, T. and Gazdar, A.: Immune cell cooperation, viruses, and antibodies to nucleic acids in New Zealand mice. J Exp Med (Supp) 134: 52-64, Sept. 1971.

647. Taranger, L.A., Chapman, W.H., Hellstrom, I. and Hellstrom, K.E.: Immunological studies on urinary bladder tumors of rats and mice. Science 176, 1337-1340, 1972.

648. Tarro, G.: Current and future studies on herpesvirus nonstructural antigens. Giorn Mal Inf Paras 23: 752-763, 1971.

649. Tarro, G.: Herpesvirus nonvirion antigens and oncogenesis. Proc 7th Mtg of the Eur Tumor Virus Group, Zierikzee, The Netherlands, 1972.

650. Tarro, G. and Battista, A.: Uncovering of complement fixing reactive groups in normal human cells. Proc 7th Mtg of the Eur Tumor Virus Group, Zierikzee, The Netherlands, 1972.

651. Tarro, G., Battista, A. and Di Gioia, M.: Studies on DF antigens of HSV: Varieties of intracellular antigens at different times after infection of cell cultures. In: Proc 16th Natl Cong Italian Soc Infect Dis, Sassari, Italy, Sept. 1971.

652. Tarro, G., Battista, A. and Manguso, L.: CF antibodies for viral and unsedimentable antigens of HSV in various kinds of human and animal sera. In: Proc 16th Natl Cong Italian Soc Infect Dis, Italy, Sept. 1971.

653. Taylor, B.A.: Strain distribution and linkage tests of 7, 12-dimethylbeutanthracene (DMBA) inflammatory response in mice. Life Sci 10: 1127-1134, 1971.

654. Taylor, B.A., Meier, H. and Myers, D.D.: Host-gene control of C-type RNA tumor virus expressions: inheritance of the group-specific antigen of murine leukemia virus. Proc Natl Acad Sci USA 68: 3190-3194, 1971.

655. Taylor, J., Templeton, A., Kyalwazi, S. and Lubega, A.: Kaposi's sarcoma in pregnancy. Brit J Surg 58: 577-599, Aug. 1971.

656. Taylor, J., Templeton, A., Vogel, C., Ziegler, J. and Kyalwazi, S.: Kaposi's sarcoma in Uganda: a clinico-pathological study. Int J Cancer 8: 122-135, July 1971.

657. Taylor, J.F., Junge, U., Wolfe, L., Deinhardt, F. and Kyalwazi, S.K.: Lymphocyte transformation in patients with Kaposi's sarcoma. Int J Cancer 8: 468-474, Nov. 1971.

658. Taylor, J.M., Faras, A.J., Varmus, H.E., Levinson, W. and Bishop, J.M.: RNA-dependent DNA synthesis by the purified DNA polymerase of RSV: characterization of the enzymatic product. Biochemistry 11: 2343-3451, June 1972.

659. Tennant, R.W.: Fate of Moloney leukemia virus in fused permissive and non-permissive cells. Bacteriol Proc 1972.

660. Tennant, R.W.: Inhibition of mitosis & macromolecular synthesis in rat embryo cells by Kilham rat virus. J Virol 8(4): 402-408, Oct. 1971.

661. Tennant, R.W., Hanna, M.G., Jr. and Thompson, S.A.: Cytotoxicity of fetal-primed spleen cells against cell cultures infected with Moloney leukemia virus. In: Embryonic and Fetal Antigens in Cancer, Vol I, AEC Symp Series, Oak Ridge, Tenn., May 1971 (N.G. Anderson and J.H. Coggin, Jr., eds.), pp 249-258.

662. Tennant, R.W., Kenney, F.T. and Tuominen, F.W.: Suppression of Moloney leukemia virus synthesis by polyadenylic acid. Proc Am Assoc Cancer Res 13: Abstr 98, 1972.

663. Tevethia, S.S., Lowry, S., Rawls, W.E., Melnick, J.L. and McMillan, V.: Detection of early cell surface changes in herpes simplex virus infected cells by agglutination with concanavalin A. J Gen Virol 15: 93-97, April 1972.

664. Theilen, G.H., Gould, D., Fowler, M., and Dungworth, D.L.: C-type virus in tumor tissues of a woolly monkey (Lagothrix spp) with fibrosarcoma. J Natl Cancer Inst 47(4): 881-889, Oct. 1971.

665. Thomas, G.F.: A method of extending electron microscope filament life. In: Proc 29th Annu Mtg of Electron Microscopy Soc of Am (C.J. Arceneaux, ed.), Claitor's Publishing Div., Baton Rouge, Louisiana, 1971, pp 52-53.

666. Thompson, K.D., Fischer, R.G. and Luecke, D.H.: Quantitative studies of avian reticuloendotheliosis virus (Strain T) in certain hematophagous arthropods. J Med Entomol 8(5): 486-490, March 1972.

667. Ting, C.C. and Herberman, R.B.: Detection of tumor specific cell surface antigen of simian virus 40-induced tumors by the isotopic antiglobulin technique. Int J Cancer 7: 499, March 15, 1971.

668. Ting, C.C. and Herberman, R.B.: Inverse relationship of tumor-specific cell surface antigens and mouse histocompatibility antigens in polyoma virus-induced tumors. Nature(New Biol) 232: 118, 1971.

669. Ting, C.C., Herberman, R.B., Lavrin, D.H. and Shiu, G.: Tumor-specific cell surface antigens in papova-virus tumors and their relationship to fetal antigens. In: Embryonic and Fetal Antigens in Cancer, Vol I, AEC Symp Series, Oak Ridge, Tenn., May 1971, (N.G. Anderson and J.H. Coggin, Jr. eds.), pp 223.

670. Ting, C.C., Lavrin, D.H., Takemoto, K.K., Ting, R.C. and Herberman, R.B.: Expression of various tumor specific antigens in polyoma virus-induced tumors. Cancer Res 32: 1, Jan. 1972.

671. Ting, R.C., Yang, S. and Gallo, R.C.: Reverse transcriptase, RNA tumor virus transformation and derivatives of rifamycin SV. Nature(New Biol) 236: 163-166, April 1972.

672. Todaro, G.J.: Cell transformation in culture: some biologic and biochemical approaches. In: Proc 9th Canadian Cancer Conf, (P.G. Scholefield, ed.), 1972, pp 176-194.

673. Todaro, G.J.: Immunological identification of the species or origin of leukemia viruses. In: Scienze and Tecnica 72, Mondadori Publishing Co., Inc., 1972, (A. Mondori, ed.), pp 67.

674. Todaro, G.J., Aaronson, S.A., Parks, W.P. and Scolnick, E.M.: Antibody to the RNA-dependent DNA polymerase of mammalian C-type RNA tumor viruses. Proc Natl Acad Sci USA 68: 920-924, 1971.

675. Todaro, G.J., Aaronson, S.A., Scolnick, E.M. and Parks, W.P.: RNA-dependent DNA polyerase in viruses and in cells. In: The Biology of Oncogenic Viruses. Amsterdam, North-Holland Publishing Co., 1971, pp 207-209.

676. Todaro, G.J. and Huebner, R.J.: The viral oncogene hypothesis: new evidence. Proc Natl Acad Sci USA 69: 1009-1015, April 1972.

677. Todaro, G.J., Scher, C. and Smith, H.: SV40 transformation and cellular growth control. In: Ciba Fdn Symp, Churchill Livingston, London, England, 1971, (G.E.W. Woltenholme and J. Knight, eds.), pp 151-167.

678. Toplin, I. and Sottong, P.: Large volume purification of tumor viruses using zonal centrifuges. Appl Microbiol 23(5): 1010-1014, May 1972.

679. Traul, K.A., Mayyasi, S.A., Garon, C.E., Schidlovsky, G. and Bulfone, L.M.: Antigenic comparison of Rauscher murine leukemia virus cultivated in human embryo and mouse cells. Proc Soc Exp Biol Med 139(1): 10-14, Jan. 1972.

680. Traul, K.A., Mitra, J., Stephens, R., Carr, D. and Woolf, D.: Chromosomal abnormalities in cells experimentally infected with Epstein-Barr virus. Bacteriol Proc 1972.

681. Trowbridge, S.T., Benyesh-Melnick, M. and Biswal, N.: Replication of the Moloney strain of murine sarcoma virus (MSV-M) in XC cells. Bacteriol Proc 1972.

682. Tsuei, D., Fujinaga, K. and Green, M.: The mechanism of viral carcinogenesis by DNA mammalian viruses: RNA transcripts containing viral and highly reiterated cellular base sequences in adenovirus-transformed cells. Proc Natl Acad Sci USA 69(2): 427-430, Feb. 1972.

683. Tuominen, F.W. and Kenney, F.T.: Inhibition of DNA polymerase of Rauscher leukemia virus by single-stranded polyribonucleotides. Proc Natl Acad Sci USA 68: 2198-2202, 1971.

684. Turner, W., Ebert, P.S., Bassin, R., Spahn, G. and Chirigos, M.A.: Potentiation of murine sarcoma virus (Harvey) (Moloney) oncogenicity in lactic dehydrogenase-elevating virus infected mice. Proc Soc Exp Biol Med 136: 1314-1318, 1971.

685. Turner, W., Ebert, P.S., Riechers, L., Pearson, J.W., and Chirigos, M.A.: Elucidation of the nature of the murine oncogenic virus inhibitor isolated from JLS-V5 cell line. Proc Soc Exp Biol Med 138(3): 1030-1034, Dec. 1971.

686. Tyndall, R.L., Otten, J.A. and Jordan, L: Altered protein profiles associated with embryogenesis and oncogenesis in mice. In: Embryonic and Fetal Antigens in Cancer, Vol I, AEC Symp Series, Oak Ridge, Tenn., May 1971, (N.G. Anderson and J.H. Coggin, Jr., eds.) pp 121-128.

687. Tyndall, R.L., Otten, J.A. Proffitt, M.R., Bowles, N.D. and Tennant, R.W.: Some similarities in the responses of mice to pregnancy and leukemogenesis. Int J Cancer 9(3): 584-594, May 1972.

688. Ubertini, T.R.: Etiological study of a lymphosarcoma in a domestic rabbit. J Natl Cancer Inst 48: 1507-1511, May 1972.

689. Ubertini, T.R.: Location of feline leukemia-sarcoma group-specific antigen in infected human tissue culture cells. Infect Immunol 5(3): 400-405, March 1972.

690. Uziel, M., Starken, J.W., Eveleight, J.W. and Johnson, W.F.: Automated sequential degradation of ribonucleic acids. Clin Chem 17: 740, 1971.

691. Valerio, D.A.: Colony management as applied to disease control with mention of some viral diseases. Lab Anim Sci 21(2): 1011-1014, 1971.

692. Valerio, D.A., Johnson, P.T. and Thompson, G.E.: Breeding the greater bushbaby, galago crassicaudatus, in a laboratory environment. Lab Anim Sci 22: 203-206, 1972.

693. Valerio, D.A., Leverage, W.E., Bensenhaver, J.C. and Thornett, H.D.: The analysis of male fertility, artificial insemination and natural matings in the laboratory breeding of macaques. In: Medical Primatology 1970, (E.I. Goldsmith and J.Moor-Jankowski, eds.), Karger/Basel, 1971, pp 515-526.

694. Van Furth, R., Gorter, M., Nadkarni, J.S., Nadkarni, J.J., Klein, E. and Clifford, P.: Synthesis of immunoglobulins by biopsed tissues and cell lines from Burkitt's lymphoma. Immunology 22: 847-857, 1972.

695. Vanky, F., Stjernsward, J., Klein, G. and Nilsonne, U.: Serum mediated inhibition of lymphocyte stimulation by autochtonous human tumors. J Natl Cancer Inst 47: 95-103, July 1971.

696. Varmus, H.E., Levinson, W.E. and Bishop, J.M.: Extent of transcription by the RNA-dependent DNA polymerase of Rous sarcoma virus (RSV). Nature(New Biol) 233: 19, 1971.

697. Varmus, H., Weiss, R., Friis, R., Vogt, P., Levinson, W. and Bishop, J.M.: Detection of avian tumor virus-specific nucleotide sequences in avian cell DNAs. Proc Natl Acad Sci USA 69(1): 20-24, Jan. 1972.

698. Vazquez, J., Albert, S., Long, A. and Soule, H.: Cultivation of cells from a pleural effusion derived from a human breast carcinoma. Proc Am Assoc Cancer Res 13: 34, 1972.

699. Vecchio, G., Tsuchida, N., Shanmugam, G., Attardi, D. and Green, M.: The detection of viral RNA in polyribosomes of cells synthesizing RNA tumor virus proteins. FASEB Mtg, Abstr, 1972, Atlantic City, New Jersey.

700. Verma, I.M., Meuth, N.L., Bromfeld, E., Manly, K.F. and Baltimore, D.: A covalently-linked RNA-DNA molecule as the initial product of the RNA tumor virus DNA polymerase. Nature(New Biol) 233: 131, 1971.

701. Verma, I.M., Temple, G.F., Fan, H. and Baltimore, D.: In vitro synthesis of DNA complementary to rabbit reticulocyte 10S RNA. Nature(New Biol) 235: 163-167, Feb. 9, 1972.

702. Vick, N.A., Bigner, D.D. and Kvedar, J.P.: The fine structure of canine gliomas and intracranial sarcomas induced by the Schmidt-Ruppin strain of the Rous sarcoma virus. J Neuropath Exp Neurol 30(3): 354-367, July 1971.

703. Viola, M., Chun, E. and Mukhophadyay, M.: Eosinophilia in patients with metastic carcinoma. Med Ann DC 41(1): 1-3, Jan. 1972.

704. Voss, W.R.: The care of baboons used in a human leukemia and oncogenic virus study. Proc 2nd Conf Exp Med & Surg in Primates, 1971, pp 1-6.

705. Voss, W.R., Buss, D.H. and Carroll, L.W.: A self-feeding device for infant baboon liquid diets. Lab Anim Sci 21(6): 901-903, Dec. 1971.

706. Wagner, S.H., Maruyama, K. and Dmochowski, L.: Tumors induced by feline viral-sarcoma in rats. Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971.

707. Wahren, B., Carlens, E., Espmark, A., Lundbeck, H., Lofgren, S., Madar, E., Henle, G. and Henle, W.: Antibodies to various herpes group viruses in sera from sarcoidosis patients. J Natl Cancer Inst 47: 747-755, July 1971.

708. Wallis, C. and Melnick, J.L.: Herpesvirus neutralization: the role of complement. J Immunol 107(5): 1235-1242, 1971.

709. Ward, J.M., Wright, J.F., Nelson, N.A., Berman, E., Liddle, C.G. and Hellman, A.: Bone and soft tissue neoplasms in cats exposed to radiostrontium. J Natl Cancer Inst 48(5): 1543-1545, May 1972.

710. Waters, L.C. and Novelli, G.D.: Analytical reversed-phase chromatography of Escherichia coli aminoacyl-tRNA. In: Methods in Enzymology 20(part C), Academic Press, New York, 1971, pp 39-43.

711. Weber, J. and Yohn, D.S.: Detection and assay of avian tumor virus group-specific antigen and antibody by the paired radio-iodine-labeled antibody technique. J Virol 9(2): 244-250, Feb. 1972.

712. Wheelock, E.F., Toy, S.T., Caroline, N.L., Sibal, L.R., Fink, M.A., Beverley, P.C.L. and Allison, A.C.: Suppression of established Friend virus leukemia by a statolon. IV. Role of humoral antibody in the development of a dormant infection. J Natl Cancer Inst 48: 665-673, March 1972.

713. Whitmire, C.E. and Huebner, R.J.: Inhibition of chemical carcinogenesis by viral vaccines. Science 177: 60-61, July 1972.

714. Whitmire, C.E. and Salerno, R.A.: RNA tumor virus gs antigen and tumor induction by various doses of 3-methylocholanthrene in various strains of mice treated as weanlings. Cancer Res 32: 1129-1132, April 1972.

715. Whitmire, C.E., Salerno, R.A., Rabstein, L.S., Huebner, R.J and Turner, H.C.: RNA tumor-virus antigen expression in chemically induced tumors. Virus-genome-specified common antigens detected by complement-fixation in mouse tumors induced by 3-methylocholanthrene. J Natl Cancer Inst 47(6): 1255-1266, Dec. 1971.

716. Williams. W.C., Shigematsu, T. and Dmochowski, L.: Immunoelectron microscopy studies on mouse mammary tumor (MTV) and mouse leukemia virus (MuLV). Proc Annu Mtg Southwest Sect Am Assoc Cancer Res, Galveston, Texas, Oct. 15-16, 1971.

717. Wolfe, L.G., Deinhardt, F., Theilen, G.H., Rabin, H., Kawakami, T. and Bustad, L.: Induction of tumors in marmoset monkeys with simian sarcoma virus type I (Lagothrix) - a preliminary report. J Natl Cancer Inst 47: 1115-1120, Nov. 1971.

718. Wolfe, L., Falk, L. and Deinhardt, F.: Herpesvirus saimiri: a simian model for potential oncogenic herpesviruses of man? Lab Invest 26: 496, 1972.

719. Wolfe, L.G., Falk, L.A. and Deinhardt, F.: Oncogenicity of herpesvirus saimiri in marmoset monkeys. J Natl Cancer Inst 47: 1145-1162, Nov. 1971.

720. Wolfe, L.G., Marczynska, B., Rabin, H., Smith, R., Tischendorf, P., Gavitt, F. and Deinhardt, F.: Viral oncogenesis in nonhuman primates. In: Med Primatol 1970, S. Karger/Basel, (E.I. Goldsmith and J. Moor-Jankowski, eds.), pp 671-682.

721. Wolfe, L.G., Smith, R. and Deinhardt, F.: Simian sarcoma virus: focus assay and susceptibility of human cells. Fed Proc 31(2): 619, Abstr 2264, Mar.-Apr. 1972.

722. Wolfe, L.G., Smith, R.K. and Deinhardt, F.: Simian sarcoma virus, type 1 (Lagothrix): focus assay and demonstration of nontransforming associated virus. J Natl Cancer Inst 48(6): 1905-1907, June 1972.

723. Woods, W.A., Turner, W. and Chirigos, M.A.: Co-infection of mouse spleen cells with murine sarcoma virus and guaroa virus. Appl Microbiol 23(2): 372-376, Feb. 1972.

724. Yang, W.K., Koh, C.K. and Waters, L.C.: Preparation of RNA-directed DNA polymerase from spleens of BALB/C mice infected with Rauscher leukemia virus. Biochem Biophys Res Commun 47: 505-511, 1972.

725. Yang, W.K. and Novelli, G.D.: Analysis of isoaccepting tRNA's in mammalian tissues and cells. In: Methods in Enzymology 20(part C), Academic Press, New York, 1971, pp 44-47.

726. Yohn, D.S. and Olsen, R.G.: Evidence of antibodies in human sera to mammalian oncornavirus antigens. Bacteriol Proc 1972.

727. Yoshida, T.O., Sekikawa, M.K., Ito, Y., Hsu, M.M., Wang, C.H., Liu, C.H. and Klein, G.: Antinuclear antibodies in sera of tumor patients in Japanese, Chinese and African (hospitals). Proc Jap Cancer Assoc 30: 139, Oct. 1971.

728. Zarling, J.M. and Tevethia, S.S.: Evidence for cell cooperation at the effector level in tumor immunity to papovavirus SV40-transformed mouse cells. Bacteriol Proc, Abstr 223, 1972.

729. Zarling, J., and Tevethia, S.S.: Expression of concanavalin A binding sites in rabbit kidney cells infected with vaccina virus. Virology 45: 313-316, July 1971.

B. PAPERS IN PRESS

730. Aaronson, S.A.: Immunologic detection of C-type RNA viral reverse transcriptase. In: Natl Cancer Inst Monograph (In Press).

731. Aaronson, S.A. and Stephenson, J.R.: Genetic factors involved in C-type RNA virus expression. In: Membrane, Viruses and Immune Mechanisms. In: Experimental and Clinical Diseases (In Press).

732. Adam, E., Correa, P., Duenas, A., Guzman, N., Iwamoto, K., Melnick, J.L., Levy, A.H. and Rawls, W.E.: Seroepidemiologic studies of herpesvirus type 2 and carcinoma of the cervix. III. Colombia. Am J Epidemiol (In Press).

733. Adam, E., Kaufman, R.H., Melnick, J.L., Levy, A.H. and Rawls, W.E.: Seroepidemiologic studies of herpesvirus type 2 and carcinoma of the cervix. III. Houston, Texas. Am J Epidemiol (In Press).

734. Allen, P.T., Bowen, J.M., Newton, W.A., East, J.L., Georgiades, J., Priori, E.S., Miller, M.F., Nash, M.A., Myers, B. and Dmochowski, L.: Molecular studies on cells derived from human solid tumors. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ of Texas, M.D. Anderson Hosp and Tumor Inst, Houston, Texas, Williams and Wilkins, Baltimore, Md. (In Press).

735. Allen, P.T., Newton, W.A., Nash, M.A., Bowen, J.M., Georgiades, J., East, J.L., Maruyama, K., Priori, E.S. and Dmochowski, L.: The role of molecular virology in the search for human RNA tumor viruses.Proc Texas Med Assoc, May 1972, San Antonio, Texas (In Press).

736. Anderson, N.G.: Fetal antigens: assay and fractionation studies. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Feb. 1972, Oak Ridge, Tenn. (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

737. Anderson, N.G.: Introduction. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Feb. 1972, Oak Ridge, Tenn. (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

738. Anderson, N.G.: Retrogenesis: problems and prospects. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Feb., 1972, Oak Ridge, Tenn. (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

739. Anderson, N.G. and Coggin, J.H., Jr. (eds.): Embryonic and Fetal Antigens in Cancer, Oak Ridge, Tenn. (In Press).

740. Aoki, T.: An analysis of antigens on the surface of murine leukemia viruses and cells. In: Unifying concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.) S. Karger, Basel, Switzerland, 1972 (In Press).

741. Aoki, T. and Johnson, P.A.: Suppression of Gross leukemia cell-surface antigens: A kind of antigenic modulation. J Natl Cancer Inst (In Press).

742. Aurelian, L.: Herpesvirus hominis: From latency to carcinogenesis? Proc 6th Annu Miles Symp on Molecular Biology, Baltimore, Md., June 1972 (In Press).

743. Aurelian, L.: The possible role of herpesvirus hominis type 2 in human cervical cancer. Fed Proc (In Press).

744. Barrett, K., Calendar, R., Gibbs, W., Goldstein, R.N., Lindquist, B. and Six, E.: Helper-dependent bacteriophage P4: A model satellite virus, and its implications for animal virology. Prog Med Virol (In Press).

745. Bassin, R.H., Phillips, L.A., Kramer, M.J., Haapala, D.K., Peebles, P.T., Nomura, S. and Fischinger, P.J.: Properties of 3T3 cells transformed by murine leukemia helper virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.) S. Karger, Basel, Switzerland 1972 (In Press).

746. Bassin, R.H., Plata, E.J., Gerwin, B.I., Mattern, C.F., Haapala, D.K. and Chu, E.W.: A human breast carcinoma cell line, HBT-3, in culture. Proc Soc Exp Biol Med (In Press).

747. Bassin, R.B., Plata, E.J., Gerwin, B.I., Mattern, C.F., Haapala, D.K. and Chu, E.W.: Isolation of a continuous epithelioid cell line, HBT-3, from a human breast carcinoma. Proc Soc Exp Biol Med (In Press).

748. Battista, A. and Tarro, G.: Effect of high and low temperatures on synthesis of complement fixing antigens in herpes simplex virus infected cell cultures. Giorn Mal Inf Parass Torino (In Press).

749. Battisto, J.R. and Lilly, F.: Hereditary aspects of the capacity to respond immunologically. In: Immunogenicity (F. Borek, ed.) (In Press).

750. Baxt, W., Hehlmann, R. and Spiegelman, S.: Human leukemic cells contain reverse transcriptase associated with a high molecular weight viral-related RNA. Nature (In Press).

751. Beard, J.W.: The avian tumor viruses. In: Ultrastructure of Animal Viruses and Bacteriophages - An Atlas (A.J. Dalton and F. Haguenau, eds.) Academic Press, Inc., New York (In Press).

752. Beard, J.W., Beard, D. and Langlois, A.J.: Etiological strain specificities of the avian tumor viruses. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

753. Bekesi, J.G. and Holland, J.F.: Combined chemotherapy and immunotherapy of transplantable and spontaneous murine leukemia. In: Recent Results in Cancer Research (G. Mathe, ed.) (In Press).

754. Bekesi, J.G., St. Arneault, G., Walter, L. and Holland, J.F.: Immunogenicity of leukemia L1210 cells after neuraminidase treatment. J Natl Cancer Inst (In Press).

755. Bergs, V.V., Pearson, G. and Chopra, H.C.: Spontaneous appearance of cytopathology and rat C-type virus in a rat embryo cell line. Int J Cancer (In Press).

756. Bernstein, R.A., Pattillo, R.A. and Hussa, R.O.: Glycogen metabolism in human hormone-producing trophoblastic cells in continuous culture. I. Characterization of BeWo glycogen phosphorylase. Comp Biochem Physiol (In Press).

757. Bikel, I. and Knight, C.A.: Differential action of Aspergillus glycosidases on the hemagglutinating and neuraminidase activities of influenza and Newcastle disease viruses. Virology (In Press).

758. Bikel, I. and Knight, C.A.: Selective removal of carbohydrate from the surface of influenza virus: effect on haemagglutinating activity of the virus. Virology (In Press).

759. Bishop, J.M., Faras, A.J., Garapin, A.C., Goodman, H., Levinson, W.E., Stavnezer, J., Taylor, J.M. and Varmus, H.E.: Characteristics of the transcription of RNA by the DNA polymerase of Rous sarcoma virus. Proc DNA Synthesis In Vitro, Steenbock Symp, July 1972 (In Press).

760. Bishop, J.M., Faras, A.J., Garapin, A.C., Hansen, C., Jackson, N., Levinson, W., Taylor, J.M. and Varmus, H.E.: RNA-directed DNA polymerase and the replication of Rous sarcoma virus. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas, Williams and Wilkins, Baltimore, Md. (J. Bowen, ed.) (In Press).

761. Bolognesi, D.P., Bauer, H., Gelderblom, H. and Molling, K.: Structural components of avian myeloblastosis virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, S. Karger, Basel, Switzerland, 1972 (In Press).

762. Boncyk, L.H. and Kalter, S.S.: Aerobic bacterial flora of chimpanzees: A four-year study. J Med Primatol (In Press).

763. Bonforte, R.J., Toplisky, M., Siltzbach, L.E. and Glade, P.R.: Phytohemagglutinin (PHA) skin test: a measure of intact cell-mediated immunity. J Pediatr (In Press).

764. Boone, C.W.: Augmented immunogenicity of tumor cell homogenates produced by infection with influenza virus. Natl Cancer Inst Monograph (In Press).

765. Bowen, J.M. and Dmochowski, L.: Inactivation of viruses by the quaternary ammonium compound, Steriquat. Proc Texas Med Assoc, May 1972, San Antonio, Texas (In Press).

766. Bowles, C.A., Hagen, W., Ditmore, J., Kerber, W.T., Woods, W.A. and Jensen, E.M.: Immunofluorescent studies of cultured canine tumor cells. Int J Cancer (In Press).

767. Bowles, C.A., Kerber, W.T., Rangan, S.R.S., Woods, W.A. and Jensen, E.M.: Studies of a transplantable canine sarcoma. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

768. Boyd, V.A.L. and Butel, J.S.: Demonstration of infectious deoxyribonucleic acid in transformed cells. I. Recovery of SV40 from yielder and non-yielder transformed cells. J Virol (In Press).

769. Brautbar, C., Payne, R. and Hayflick, L.: Fate of HL-A antigens in human diploid cell strains in vitro after continuous cultivation. Exp Cell Res (In Press).

770. Brodsky, A.L. and Heath, C.W.: Infectious mononucleosis: epidemiologic patterns at U.S. colleges and universities. Am J Epidemiol (In Press).

771. Bryan, R.J. and Gordon, R.J.: Composition of particles in Los Angeles air. Environ Sci Tech (In Press).

772. Bryan, W.R.: Section 1. Etiology of cancer: Introduction. In: Cancer Medicine (J.F. Holland and E. Frei, III, eds.), Lea and Febiger, Philadelphia (In Press).

773. Butel, J.: Infectious nucleic acids of tumor viruses. Methods Cancer Res (In Press).

774. Butel, J.S. and Melnick, J.L.: The state of the viral genome in cells transformed by Simian virus 40: a review. Exp Mol Pathol (In Press).

775. Caffier, H., Parson, J.T. and Green, M.: Mechanism of viral carcinogenesis by DNA mammalian viruses. IX. Transcription of the adenovirus type 7 genome during productive infection and in transformed cells. J Mol Biol (In Press).

776. Canaani, E. and Duesberg, P.H.: The preferred role of 60-70S avian tumor virus RNA among natural RNA's as template for DNA polymerase of Rous sarcoma virus (RSV). In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas, March 1972, (J. Bowen, ed.), Williams and Wilkins, Baltimore, Md. (In Press).

777. Canaani, E. and Duesberg, P.H.: Role of subunits of 60-70S avian tumor virus RNA in its template activity for the viral DNA polymerase. J Virol (In Press).

778. Chen, H.W., Meier, H., Heiniger, H.J. and Huebner, R.J.: Tumorigenesis in strain DW/J mice and the induction of the endogenous C-type RNA tumor virus group-specific antigen by prolactin. J Nat Cancer Inst (In Press).

779. Chirigos, M.A., Pearson, J., Spahn, G. and Rutman, R.: Current studies on oncorna virus therapy. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

780. Chopra, H.C.: Oncorna type virus particles in a tumor of a rhesus monkey. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

781. Chopra, H., Fine, D., Pienta, R. and Woodside, N.: Studies on oncogenic properties of a virus isolated from the monkey breast tumor. In: Medical Primatol (In Press).

782. Chopra, H.C. and Oie, H.K.: Possible etiological role of virus particles detected in rat and monkey mammary carcinomas. J Natl Cancer Inst (In Press).

783. Churchill, W.H., Jr., Rocklin, R.E., Moloney, W.C. and David, J.R.: In vitro evidence of normal lymphocyte functions in some patients with Hodgkin's disease and negative delayed cutaneous hypersensitivity. Natl Cancer Inst Monograph (In Press).

784. Cochran, A., Klein, E. and Kiessling, R.: The effect of immune factors on the motility and spread of lymphoma cells. J Natl Cancer Inst (In Press).

785. Coggin, J.H., Jr.: Fetal antigens: in vitro and in vivo characterization. In: Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Feb. 1972, Oak Ridge, Tenn. (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

786. Coggin, J.H., Jr. and Ambrose, K.R.: Phase specific surface autoantigens on membranes of fetus and tumors. Proc 4th Int Conf on Lymphatic Tissue and Germinal Centers in Immune Reactions, Dubrovnik, Yugoslavia, June 1972 (In Press).

787. Coggin, J.H., Jr., Ambrose, K.R., Bellomy, B.B. and Anderson, N.G.: Fetal antigen capable of inducing transplantation immunity against tumor. In: Yearbook of Cancer (R.W. Cumley, ed.) (In Press).

788. Collins, M.J., Jr. and Parker, J.C.: Murine virus contaminants of leukemia viruses and transplantable tumors. J Natl Cancer Inst (In Press).

789. Dabich, L., Bookstein, J.J., Zweifler, A.J. and Zarafonetis, C.J.D.: Digital arteries in patients with scleroderma: an arteriographic and plethysmographic study. Arch Intern Med (In Press).

790. Dales, S. and Hanafusa, H.: Penetration and intracellular release of the genomes of avian RNA tumor viruses. Virology (In Press).

791. Dalton, A.J.: RNA tumor viruses-terminology and ultrastructural aspects of virion morphology and replication. J Natl Cancer Inst (In Press).

792. Dalton, A.J. and Haguenau, F.J. (eds.): Ultrastructure of Animal Viruses and Bacteriophages--An Atlas. Academic Press, Inc., New York, New York (In Press).

793. Deinhardt, F., Falk, L., Marczynska, B., Shramek, G. and Wolfe, L.: Herpesvirus saimiri: a simian counterpart of Epstein-Barr virus of man? In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp Cancer Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

794. Deinhardt, F., Wolfe, L., Massey, R., Hoekstra, J. and McDonald, R.: Simian sarcoma virus: oncogenicity, focus assay, presence of associated virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

795. Deinhardt, F., Wolfe, L., McDonald, R. and Hoekstra, J.: Feline, avian and simian virus-induced neoplasia in marmoset monkeys: a comparison. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

796. Dennert, G. and Lennox, E.: Cell interactions in humoral and cell-mediated immunity. Nature (New Biol) (In Press).

797. Dennert, G. and Lennox, E.: Lymphoid cell interactions in cell mediated immunity. Proc 4th Int Conf on Lymphatic Tissue and Germinal Centers in Immune Reactions, Dubrovnik, Yugoslavia, June 1972 (In Press).

798. DeThe, G.: Etiology of Burkitt's Lymphoms. Cancer Res (In Press).

799. DeThe, G.: The etiology of nasopharyngeal carcinoma. In: Pathobiology Annual 1972, Appleton, Century Crofts, Meredith Corp., New York (In Press).

800. DeThe, G. and Geser, A.: A prospective sero-epidemiological study to investigate the role of EBV in Burkitt's lymphoma. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.) (In Press).

801. DeThe, G., Geser, A. and Ay, N.: Problems raised by the association of a herpes virus with two different human tumours: Burkitt's lymphoma and nasopharyngeal carcinoma. Proc Int Cancer Conf, March 1972, Sydney, Australia (In Press).

802. Dion, A.S., Sarkar, N.H. and Moore, D.H.: An attempt to correlate RNA-templated DNA polymerase activity with virus-like particles in human milk: Murine mammary tumor (MuMTV) as a model system. Proc 6th Annu Miles Int Symp Molecular Biology, Baltimore, Maryland (In Press).

803. DiSaia, P.J., Sinkovics, J.G., Rutledge, F.N. and Smith, J.P.: Cell-mediated immunity to human malignant cells. A Brief review and further studies with two gynecologic tumors. Amer J Obstet Gynecol (In Press).

804. Dmochowski, L.: The search for virus in human cancer. Proc 7th Natl Cancer Conf, Los Angeles, California, Sept. 1972 (In Press).

805. Dmochowski, L.: Studies on the interrelationship of type B and type C virus particles in breast cancer and in leukemia. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

806. Dmochowski, L.: Unifying concepts of leukemia and related neoplasms in animals and man leading to eventual control and prevention. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

807. Dmochowski, L., Allen, P.T., Bowen, J.M., East, J.L., Georgiades, J., Maruyama, K. and Newton, W.A., Jr.: Studies on transforming activities from human solid tumor cells following co-cultivation with human leukemic bone marrow cells. Proc 6th Annu Miles Int Symp on Molecular Biology, Baltimore, Md., June 1972 (In Press).

808. Dmochowski, L., Bowen, J.M., Allen, P.T., East, J.L., Georgiades, J., Maruyama, K. and Newton, W.A., Jr.: Implication of animal model systems in studies on the relationship of viruses to human leukemia and solid tumors. Proc Symp on Viral Tumorigenesis and Immunogenesis, University Park, Pennsylvania, April 1972 (In Press).

809. Dmochowski, L., East. J.L., Bowen, J.M., Lewis, M.L. and Shigematsu, T.: Studies on tumorigenicity of rat bone tumor virus (SD-MSV-M) in mice, rats, and hamsters. Tex Rep Virol Med (In Press).

810. Dmochowski, L., Lewis, M.L., Shigematsu, T., Bowen, J.M. and East, J.: Studies on tumorigenicity of rat bone tumor virus (SD-MSV-M) in mice, rats and hamsters. Tex Rep Biol Med (In Press).

811. Dmochowski, L., Shigematsu, T. and Williams, W.C.: Immunoelectron microscopy studies of mouse mammary tumor virus (MTV). J Nat Cancer Inst (In Press).

812. Docherty, J.J., Mantyjarvi, R.A. and Rapp, F.: Mechanism of the restricted growth of herpes simplex virus type 2 in a hamster cell line. J Gen Virol (In Press).

813. Dosik, H. and Madahar, P.: Fluorescent banding of Y chromosomes in normal humans. Am J Human Genet (In Press)

814. Dosik, H., Madahar, P. and Ehlin, M.: Identification of human chromosomes with wuinacrine mustard: a new photographic technique. Am J Human Genet (In Press).

815. Dressman, G.R., Suriano, J.R., Swartz, S.K. and McCombs, R.M.: Characterization of the herpes virion. I. Purification and amino acid composition of nucleocapsids. Virology (In Press).

816. Duesberg, P.H.: RNA tumor virus replication: facts and fancy. Proc Schering Workshop on Genetic Engineering, Feb. 1972 (In Press).

817. Duesberg, P.H., Vogt, P.K. and Martin, G.S.: The 60-70S RNA of avain sarcoma and leukosis viruses: distribution of class a and b subunits. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

818. Duff, R. and Rapp, F.: The induction of oncogenic potential by herpes simplex viruses. In: Proc Gustav Stern Symp on Perspectives in Virology (In Press).

819. Dunkel, V.C., Frankel, L.D., Fowler, A.K. and Hellman, A.: Serological patterns to EBV-associated antigens in a patient with infectious mononucleosis. New Engl J Med (In Press).

820. Dunkel, V.C. and Myers, S.L.: Continuous lymphoblastoid cell line from a rhesus monkey with myelogenous leukemia. J Natl Cancer Inst 1972 (In Press).

821. Dunkel, V.C., Pry, T.W., Henle, G. and Henle, W.: Immunofluorescence test for antibodies to Epstein-Barr virus (EBV) with sera of lower primates. J Natl Cancer Inst (In Press).

822. Dutcher, R.M.: The improtance of animal studies in the development of means for prevention and control of leukemia. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

823. Dutcher, R.M. and Chieco-Bianchi, L. (eds.): Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, S. Karger, Basel, Switzerland, 1972 (In Press).

824. Dvorak, H.G., Dvorak, A.M. and Churchill, W.H.: Basophilic leukocytes in the immunologic rejection of diethylnitrosamine (DEN) induced hepatomas in strain-2 guinea pigs. Fed Proc (In Press).

825. Eckhart, W.: Cell transformation by polyoma virus and SV40. Curr Top Oncol (In Press).

826. Eckhart, W. Oncogenic Viruses. Annu Rev Biochem (In Press).

827. Engelstein, J.M., Herberman, R.B. and Waltman, S.R.: Protection of penetrating corneal allografts from immune rejection. Am J Opthamol (In Press).

828. Ernberg, I.: Epstein-Barr virus induced antigens and macromolecular synthesis in human, EBV-infected lymphoblastoid cell lines. Proc Symp 7th FEBS Mtg, 1971, Varna (In Press).

829. Essex, M.: Role of the immune response in the development and progression of virus-induced tumors of cats. J Am Vet Assoc (In Press).

830. Essex, M., Klein, G., Deinhardt, F., Wolfe, L.G., Hardy, W.D., Jr., Theilen, G.H. and Pearson, L.D.: Induction of the feline oncornavirus-associated cell membrane antigen in human cells. Nature (In Press).

831. Essex, M., Snyder, S.P. and Klein, G.: Relationship between humoral antibodies and the failure to develop progressive tumors in cats injected with feline sarcoma virus (FSV). In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland (In Press).

832. Evans, D.L., Barnett, J., Bowen, J.M. and Dmochowski, L.: Antigenic relationship between the herpes viruses of infectious bovine rhinotracheitis, Marek's disease and Burkitt's lymphoma. J Virol (In Press).

833. Evans, D.L., Barnett, J. and Dmochowski, L.: Common antigens in three herpes-type virus-associated diseases. Proc Texas Med Assoc, May 1972, San Antonio, Texas (In Press).

834. Eveleigh, J.W.: Extracellular glycoproteins from transformed cells. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Feb. 1972, Oak Ridge, Tenn. (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

835. Falk, L.A., Wolfe, L.G. and Deinhardt, F.: Epidemiology of herpesvirus saimiri (HSV) infection in squirrel monkeys. Proc 3rd Conf on Exptl Med and Surg in Primates, S. Karger, Basel, New York (In Press).

836. Feller, W.F. and Kantor, J.: The clinical status of women whose milk contains reverse transcriptase and 70S RNA. Proc 7th Int Mtg on Breast Cancer in Animals and Man, Grenoble, France, June 1972 (In Press).

837. Ferrer, J.F.: Bovine C-type virus: antigenic comparison with murine and feline leukemia viruses. Cancer Res (In Press).

838. Ferrer, J.F., Avila, L. and Stock, N.D.: Recent electron microscopic and immunological studies on bovine cell cultures containing C-type viruses. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

839. Ferrer, J.F., Avila, L. and Stock, N.D.: Serological detection of C-type viruses found in bovine cultures. Cancer Res (In Press).

840. Ferrer, J.F., Fuillemain, B. and Stock, N.D.: Tissue culture conditions affecting the expression of latent C-type viruses in leukemia. Proc 14th Int Cong Hematology, July 1972, Sao Paulo, Brazil (In Press).

841. Fine, D.L., Kingsbury, E.W., Valerio, M.G., Kubicek, M.T., Landon, J.C. and Chopra, H.C.: Simian tumor virus proliferation in inoculated Macaca mulatta. Nature (In Press).

842. Fine, D.L., Pienta, R.J., Valerio, M.G. and Chopra, H.C.: Current studies on a virus isolated from a breast carcinoma of rhesus monkey. Proc 7th Mtg on Breast Cancer in Animals and Man, Grenoble, France, June 1972 (In Press).

843. Fischer, R.G.: Friend leukemia virus (FLV) activity in certain arthropods: I. Introduction: Parameters and control measures necessary for evaluation of extrinsic incubation potential. Neoplasm (In Press).

844. Fowler, A.K., Hellman, A. and Dimmick, R.L.: Environmental pollutants as activators of C-type RNA tumor virus information. IVth Int Symp on Aerobiology (In Press).

845. Fowler, A.K. and Reed, C.D.: Estrogen analysis of neonatal bovine urine using gas-liquid chromatography. J Anim Sci (In Press).

846. Fowler, A.K., Reed, C.D., Todaro, G.J. and Hellman, A.: Activation of C-type RNA virus markers in mouse uterine tissue. Proc Natl Acad Sci USA (In Press).

847. Fowler, A.K., Steinman, H.G., Reed, C.D. and Hellman, A.: Studies of the blastogenic response of murine lymphocyte. IV. Endocrinological effects. Proc Soc Exp Biol Med (In Press).

848. Freeman, A.E., Price, P.J., Zimmerman, E.M., Kelloff, G.J. and Huebner, R.J.: RNA tumor virus genomes as determinants of chemically induced transformation in vitro. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

849. Friberg, S., Jr.: Comparison of an immunoresistant and an immunosusceptible ascites subline from the murine tumor TA3. I. Transplantability, morphology and some physiochemical characteristics. J Natl Cancer Inst (In Press).

850. Friberg, S., Jr.: Comparison of an immunoresistant and an immunosusceptle ascites subline from the murine tumor TA3. II. Immuno-sensitivity and antibody binding capacity in vitro, and immunogenicity in allogeneic mice. J Natl Cancer Inst (In Press).

851. Friberg, S., Jr., Golub, S., Lilliehook, B. and Cochran, A.: Assessment of concanavilin A reactivity to murine ascites tumors by inhibition of tumor cell migration. Exp Cell Res (In Press).

852. Gail, M.H. and Boone, C.W.: Procaine inhibition of fibroblast motility and proliferation. Exp Cell Res (In Press).

853. Gardner, M.B., Charman, H.P., Johnson, E.Y., Rongey, R.W., Gilden, R.V., Arnstein, P. and Huebner, R.J.: Natural history studies of the feline RNA tumor virus genome. I. Detection of group specific antigen and C-type particles. Proc XII Int Cong Biol Standardization (In Press).

854. Gardner, M.B., Officer, J.E., Rongey, R.W., Charman, H.P., Hartley, J.W., Estes, J.D. and Huebner, R.J.: C-type RNA tumor virus in wild house mice (Mus musculus). In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

855. Gatti, R.A., Kersey, J.H., Yunis, E.J. and Good, R.A.: Graft-versus-host disease. In: Prog Clin Pathol 4 (D. Yi-Yung-Hsia, ed.), Grune and Stratton, New York (In Press).

856. Gazdar, A.F., Steinberg, A.D., Spahn, G.J. and Baron, S.: Virus-induced sarcoma and leukemia: Enhancement in mice and cats by several interferon inducers. Proc Soc Exp Biol Med (In Press).

857. Gelderblom, H., Bauer, H., Bolognesi, D.P. and Frank, H.: Morphogenese und aufbau von RNA-tumorviren: Elektronenoptische untersuchungen an virus-partikeln vom C-typ. Zibl Bakt I. Orig. (In Press).

858. Gerwin, B.I. and Milstein, J.B.: An oligonucleotide affinity column for RNA-dependent DNA polymerase from RNA tumor viruses. Proc Natl Acad Sci USA (In Press).

859. Gilden, R.V.: Co-evolution of RNA tumor virus genome and vertebrate host genes. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas, March 1972, (J. Bowen, ed.) Williams and Wilkins, Baltimore, Maryland (In Press).

860. Gilden, R.V. and Oroszlan, S.: Group specific antigens of RNA tumor viruses as markers for subinfectious expression of the RNA virus genome. Proc Nat Acad Sci USA (In Press).

861. Girardi, A.J.: Antigens in neoplastic tissue. In: Natl Cancer Inst Monograph, Immunology of Carcinogenesis (In Press).

862. Girardi, A.J. and Repucci, P.: Relationship of hamster fetal antigen to SV40 tumor specific transplantation antigen. In: Embryonic and Fetal Antigens in Cancer, Vol. 2, AEC Symp Series, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, eds.) (In Press).

863. Glaser, R. and Rapp, F.: Rescue of Epstein-Barr virus from somatic cell hybrids of Burkitt lymphoblastoid cells. J Virol (In Press).

864. Goldberg, R.J., Docherty, J.J. and Rapp, F.: Inhibition of synthesis of herpes simplex virus deoxyribonucleic acid by a carcinogenic polycyclic aromatic hydrocarbon. Proc Soc Exp Biol Med (In Press).

865. Golstein, P., Svedmyr, E.A.J. and Blomgren, H.: Specific adsorption of cytotoxic thymus-processed lymphocytes (T cells) on glutaraldehydefixed fibroblast monolayers. Nature (In Press).

866. Golub, S.H., Hewetson, J.F., Svedmyr, E.A.J., Klein, G. and Singh, S.: Studies on cell-mediated reactions against cultured Burkitt lymphoma cells. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

867. Golub, S.H., Hewetson, J.F., Svedmyr, E.A.J. and Singh, S.: Cellular reactions against Burkitt lymphoma cells. II. Effector cells obtained by allogeneic stimulation in mixed leukocyte cultures. Int J Cancer (In Press).

868. Golub, S.H., Svedmyr, E.A.J., Hewetson, J.F., Klein, G. and Singh, S.: Cellular reactions against Burkitt lymphoma cells. III. Effector cell activity of leukocytes stimulated in vitro with autochthonous cultured lymphoma cells. Int J Cancer (In Press).

869. Graham, H., Coley, R. and Lilly, F.: Genetic control of the antibody response to the H-2.2 alloantigen in mice. Proc Transplantation Society Congress, Sept. 1972 (In Press).

870. Green, M.: Inhibition of DNA polymerases of RNA tumor viruses and cells by rifampicin derivatives. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

871. Green, M., Parson, J.T., Caffier, H., Landgraf-Leurs, M. and Tsuei, D.: Transcription of adenovirus genes in productively infected and in transformed cells. In: The Biology of Oncogenic Viruses, Proc 2nd Lepetit Colloq, North-Holland Pub. Co., Amsterdam (In Press).

872. Green, M. and Raskas, H.J.: Molecular hybridization: a powerful approach to the detection of viral nucleic acid sequences in human cancer. J Natl Cancer Inst (In Press).

873. Grundner, G., Fenyo, E.M., Strouk, V. and Klein, E.: Murine leukemia virus assay techniques: a comparative study. Proc Soc Exp Biol Med (In Press).

874. Gulati, S.C., Axel, R. and Spiegelman, S.: The detection of reverse transcriptase and high molecular weight RNA in malignant tissue. Proc Natl Acad Sci USA (In Press).

875. Gunven, P.: EBV-associated antibody titers in Burkitt's lymphoma and other diseases. Proc Symp on Viral Aetiology of Human Cancer, Rome, 1972 (In Press).

876. Gunven, P., Klein, G., Henle, G., Henle, W., Clifford, P, and Singh, S.: Antibodies to Epstein-Barr virus associated antigens in Burkitt's lymphoma. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

877. Gurgo, C., Ray, R. and Green, M.: Rifamycin derivatives which strongly inhibit RNA-DNA polymerase (reverse transcriptase) of murine sarcoma viruses. J Natl Cancer Inst (In Press).

878. Hackett, A.J., Sylvester, S.S. and Calvin, M.: A cell line derived from BALB/3T3 cells: a substrate for murine leukemia virus assay and for quantitative studies on the transformation of cells. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas (J. Bowen, ed.) Williams and Wilkins, Baltimore, Maryland (In Press).

879. Halliday, W.J.: Macrophage migration inhibition with mouse tumor antigens: properties of serum and peritoneal cells during tumor growth and after tumor loss. Cell Immunol (In Press).

880. Hampar, B.: Immunological relationships. In: The Herpesviruses, Academic Press, New York (In Press).

881. Hanafusa, H., Baltimore, D., Smoler, D., Watson, K.F., Yaniv, A. and Spiegelman, S.: Absence of polymerase protein in virions of alpha-type Rous sarcoma virus. Science (In Press).

882. Hanna, M.G., Jr., Nettesheim, P., Richter, C.B. and Tennant, R.W.: The variable influence of the microflora and intercurrent infections on immunologic competence and carcinogenesis. In: Immunological Parameters of Host-tumor Relationships (D.W. Weiss, ed.), Academic Press, New York (In Press).

883. Hanna, M.G., Jr., Tennant, R.W., Yuham, J.M., Clapp, N.K., Batzing, B.L. and Snodgrass, M.J.: Autogenous immunity to endogenous RNA-tumor virus antigens in mice with a low natural incidence of lymphoma. Cancer Res (In Press).

884. Hanna, M.G., Jr., Zbar, B. and Rapp, H.J.: Histopathology of tumor regression following intralesional injection of mycobacterium bovis (BCG). I. Tumor growth and metastasis. J Natl Cancer Inst (In Press).

885. Harter, D.H., Schlom, J., Burny, A. and Spiegelman, S.: Visna virus: a 'slow' neurotropic agent with tumor virus properties. Trans Amer Neurol Assoc (In Press).

886. Hatanaka, M., Twiddy, E. and Gilden, R.V.: Protein kinase associated with RNA tumor viruses and other budding RNA viruses. Virology (In Press).

887. Hayflick, L.: Mycoplasmas as pathogens. In: Pathogenic Mycoplasmas, CIBA Fdn. Symp., 1972 (In Press).

888. Heath, C.W., Jr.: The epidemiology of Hodgkin's disease (editorial). Ann Intern Med (In Press).

889. Heath, C.W., Jr. and Evatt, B.L.: Observations concerning the time-space distribution of childhood acute leukemia in DeKalb County, Georgia. Proc 6th Annu Conf on Trace Substances in Environmental Health (In Press).

890. Hehlmann, R., Kufe, D. and Spiegelman, S.: Viral-related RNA in Hodgkin's disease and other human lymphomas. Proc Natl Acad Sci USA (In Press).

891. Heine, U.I. and Dalton, A.J.: Ultrastructural analysis of herpes-type viruses. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

892. Hellman, A., Fowler, A.K., Steinman, H.G. and Buzzerd, P.M.: Studies of the blastogenic response of murine lymphocyte. III. Specific viral transformation. Proc Soc Exp Biol Med (In Press).

893. Hellstrom, I. and Hellstrom, K.E.: Cell-mediated immunity and "blocking" antibodies to renal allografts. Transpl Proc (In Press).

894. Hellstrom, I. and Hellstrom, K.E.: Murine bladder tumors as models for human tumor immunity. J Natl Cancer Inst (In Press).

895. Hellstrom, I. and Hellstrom, K.E.: Some aspects of human tumor immunity and their possible implications for tumor prevention and therapy. In: Frontiers in Radiation Therapy and Oncology, S. Karger (In Press).

896. Hellstrom, I. and Hellstrom, K.E.: Some comments on the role of blocking serum factors in tolerance to allografts. Proc Conf Cell Antigens, Philadelphia, 1971, Springer Verlag (In Press).

897. Hellstrom, I. and Hellstrom, K.E.: Some recent studies on cellular immunity to human melanomas. Fed Am Soc Exp Biol (In Press).

898. Hellstrom, K.E. and Hellstrom, I.: Cellular immunity to tumor antigens - possible clinical usefulness of the findings so far obtained. Proc Conf Cellular Antigens, Philadelphia, 1971, Springer Verlag (In Press).

899. Hellstrom, K.E. and Hellstrom, I.: Cytotoxic lymphocytes, blocking serum factors and "unblocking" antibodies in cancer patients. Proc Symp on Membranes, Viruses and Immune Mechanisms in Exp and Clin Dis, Univ. of Minnesota, 1972, Academic Press, New York (In Press).

900. Hellstrom, K.E. and Hellstrom, I.: On the role of serum factors "unblocking antibodies" as mediators of immunological nonreactivity to cellular antigens. Proc CIBA Foundation Symp Ontogeny of Acq Immun, Williams and Wilkins, Baltimore, Maryland (In Press).

901. Helmke, R.J., Heberling, R.L. and Kalter, S.S.: Growth characteristics and viral susceptibility of a chimpanzee (pan troglodytes) lung diploid cell line, SFRE: CL-1. Proc Soc Exp Biol Med (In Press).

902. Henle, W. and Henle, G.: Die beziehung des Epstein-Barr-virus zur infectiosen mononukleose und zu verschiedenen menschilichen tumoren. Robert-Koch-Preis Vorlesung, Bonn-Bad Godesberg, Dec. 1971 (In Press).

903. Henle, W. and Henle, G.: Epstein-Barr virus (EBV)-related serology in Hodgkin's disease. Proc Int Symp on Hodgkin's Dieseas, Stanford Univ., Stanford, California, March 1972 (In Press).

904. Herberman, R.B.: Cellular immunity to human tumor associated antigens. Israel J Med Sci (In Press).

905. Herberman, R.B.: Immunological aspects observed in childhood malignancies; rationale for immunotherapy of these tumors. Proc Radiotherapy Symp., Clinical Pediatric Oncology (In Press).

906. Herberman, R.B.: In vivo and in vitro assays of cellular immunity to human tumor antigens. Fed Proc 1972 (In Press).

907. Herberman, R.B.: In vivo mehtods: Delayed hypersensitivity response toward autochthonous tumor extracts. Proc Coll of the Centre National de la Recherch Scientifique on The Investigation and Stimulation of Immunity in Cancer Patients (In Press).

908. Herberman, R.B., Hollinshead, A.C., Alford, T.C., McCoy, J.L., Halterman, R.H. and Leventhal, B.G.: Delayed cutaneous hypersensitivity to reactions to extracts of human tumors. J Natl Cancer Inst (In Press).

909. Herberman, R.B. and Rosenberg, E.B.: Cellular cytotoxicity reactions to human leukemia associated antigens. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

910. Herberman, R.B., Rosenberg, E.B., Halterman, R.H., McCoy, J.L. and Leventhal, B.G.: Cellular immune reactions to human leukemia. Proc Immunology of Carcinogenesis Mtg. In: Natl Cancer Inst Monograph (In Press).

911. Hewetson, J.F., Golub, S.H., Klein, G. and Singh, S.: Cellular reactions against Burkitt lymphoma cells. I. Colony inhibition with effector cells from patients with Burkitt's lymphoma. Int J Cancer (In Press).

912. Hilleman, M.R.: Perspectives in the control of viral diseases including cancer. Proc Oholo Biological Conf., Zichron Yaakov, Israel (In Press).

913. Hilleman, M.R.: Problems and potentials for human viral cancer vaccines. Preventive Med (In Press).

914. Hilleman, M.R.: Viral vaccines and the control of cancer. Proc Gustav Stern Symp on Perspectives in Virology, No. 8, Academic Press, New York (In Press).

915. Hoggan, M.D. and Thomas, G.R.: Australia Antigen. In: Ultrastructure of Animal Viruses and Bacteriophages--An Atlas. (A.J. Dalton and F.J. Haguenau, eds.), Academic Press, Inc., New York, New York (In Press).

916. Hollinshead, A.C. and Herberman, R.B.: Separation of the major histocompatibility antigens from other antigens present on human leukemic and white blood cell membranes. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

917. Hollinshead, A.C., Herberman, R.B. and Alford, T.C.: Soluble membrane antigens of human malignant melanoma cells. Cancer (In Press).

918. Hollinshead, A.C., Lee, O.B., McKelway, W., Melnick, J.L. and Rawls, W.E.: Reactivity between herpesvirus type 2-related soluble cervical tumor cell membrane antigens and matched cancer and control sera. Proc Soc Exp Biol Med (In Press).

919. Hollinshead, A.C., McCammon, J.R. and Yohn, D.S.: Immunogenicity of a soluble transplantation antigen from adenovirus-12-induced tumour cells demonstrated in inbred hamsters (PD-4). Can J Microbiol (In Press).

920. Hollinshead, A.C., McWright, J.G., Alford, T.C. and Glew, D.: Separation of skin-reactive intestinal cancer antigen from the carcinoembryonic antigen of Gold. Science (In Press).

921. Horst, J., Content, J., Mandeles, S., Fraenkel-Conrat, H. and Duesberg, P.H.: Distinct oligonucleotide patterns of distinct influenza virus RNA's. J Molec Biol (In Press).

922. Huebner, R.J., Freeman, A.E., Whitmire, C.E., Price, P.J., Rhim, J.S. Kelloff, G.J., Gilden, R.V. and Meier, H.: Endogenous and exogenous RNA tumor virus genomes in chemical carcinogenesis. In: Monograph of 24th Annu. Symp. Fund. Cancer Res., Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., 1971 (In Press).

923. Huebner, R.J. and Gilden, R.V.: Inherited RNA viral genomes (virogenes and oncogenes) in the etiology of cancer. In: RNA viruses and Host Genome in Oncogenesis (P. Emmelot and P. Bentvelsen, eds.), North Holland Publishing Co., Amsterdam (In Press).

924. Hull, R., Dwyer, A., Holmes, A., Nowakowski, E., Deinhardt, F., Lennette, E. and Emmons, R.: Recovery and characterization of a new simian herpesvirus from a fatally infected spider monkey. Pan Amer Health Organization Sci Bull (In Press).

925. Hussa, R.O. and Pattillo, R.A.: Effects of methotrexate on established cell lines of human choriocarcinoma in vitro. Europ J Cancer (In Press).

926. Inbar, M., Ben-Bassat, H. and Sachs, L.: Inhibition of ascites tumor development by concanavalin A. Int J Cancer (In Press).

927. Inbar, M., Vlodavsku, I. and Sachs, L.: Availability of L-fucose-like sites on the surface membrane of normal and transformed mammalian cells. Biochem Biophys Acta (In Press).

928. Ishimoto, A. and Ito, Y.: Presence of antibody against mouse fetal antigen in the sera from C57/BL6 mice immunized with Rauscher leukemia. Cancer Res (In Press).

929. Jagarlamoody, S.M., Bearon, A.H. and McKhann, C.F.: Comparison of anti-lymphocyte serum and antiplasma cell serum: Effect on induction and transplantation of tumors. Proc 4th Int Congress of Transplantation Soc, Sept. 1972 (In Press).

930. Jakobsson, H. and Blomgren, H.: Changes of the PHA-responsive pool of cells in the thymus following cortisone or X-ray treatment of mice. Evidence for an inverse relation between the production of cortical and medullary thymocytes. Cell Immunol (In Press).

931. Johnson, T.R.: Lymphocyte and antibody cytotoxicity to tumor cells measured by a micro-51 chromium release assay. Immunological Communications (In Press).

932. Kalter, S.S.: Significance of simian viruses. Proc Nat Conf Res Animals in Med (In Press).

933. Kalter, S.S.: Virus Research. In: Primates in Biomedical Research (G. Bourne, ed.) (In Press).

934. Kalter, S.S., Eichberg, J., Heberling, R.L. and Felsbury, P.J.: Detection of viruses in nonhuman primate tissues by use of explants. Proc 12th Int Cong Biological Standardization, Annecy, Sept. 1971, S. Karger, Basel, Switzerland (In Press).

935. Kalter, S.S., Heberling, R.L. and Ratner, J.J.: EBV antibody in sera of non-human primates. Nature (In Press).

936. Kaplan, A.S. (ed.): Immunological Relationships. In: The Herpesviruses. Academic Press, New York (In Press).

937. Kawakami, T.G., Buckley, P.M. and Huff, S.D.: Characterization of a C-type virus associated with gibbon lymphosarcoma. Proc 3rd Conf on Exp Med and Surg in Primates, Lyon, France, June 1972, S. Karger, New York (In Press).

938. Kawakami, T.G., Buckley, P.M. and Huff, S.D.: Comparative characterization of C-type viral isolates from spontaneous simian sarcoma and leukemia. Proc Int Cancer Conf, March 1972, Sydney, Australia (In Press).

939. Kawakami, T.G., Buckley, P.M., Huff, S., McKain, D. and Fielding, H.: A comparative study in vitro of a simian virus isolated from spontaneous woolly monkey fibrosarcoma and of a known feline fibrosarcoma virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

940. Kawakami, T.G., Huff, S.D., Buckley, P.M., Dungworth, I.L., Snyder, S.P. and Gilden, R.V.: Isolation and characterization of a C-type virus associated with gibbon lymphosarcoma. Nature (In Press).

941. Kelloff, G.J., Huebner, R.J. and Gilden, R.V.: Isolation and characterization of the hamster C-type viruses. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

942. Kelloff, G.J., Long, C. and Gilden, R.V.: Production of cell hybrids of human leukemic lymphocytes and HT-1 cells. Nature (In Press).

943. Kenney, F.T., Lee, K.L. and Barker, K.L.: Hormonal mechanisms in regulation of gene expression. In: Proc 11th Int Latin-Amer Symp, La Plata, Argentina, Nov.-Dec., 1971, Plenum Press, New York (In Press).

944. Kenney, F.T., Lee, D.L. and Stiles, C.D.: Degradation of messenger RNA in mammalian cells. Proc 5th Karolinska Symp, Gene Transcription in Reproductive Tissue (E. Diczfalusy and A. Diczfalusy, eds.), Karolinska Institutet, Stockholm, Sweden, 1972 (In Press).

945. Kersey, J.H. and Good, R.A.: Surveillance mechanisms and malignancy. Proc Bell Symp (In Press).

946. Keydar, J., Gilead, Z., Karby, S. and Harel, E.: Production of virus by embryonic cultures co-cultivated with breast tumor cells or infected with milk from breast cancer patients. Proc 7th Int Mtg on Breast Cancer in Animals and Man, Grenoble, France, June 1972 (In Press).

947. Kinard, R. and Rabin, H.: Oncogenic virus studies in nonhuman primates under the Special Virus Cancer Program. Proc 3rd Conf on Exp Med and Surg in Primates, Lyon, France, June 1972, S. Karger, New York (In Press).

948. Klein, E. and Klein, G.: Significance of the cellular antigens in Burkitt's lymphoma. Conf Cellular Antigens, Philadelphia (In Press).

949. Klein, E. and Klein, G.: Specificity of homograft in vivo, assessed by inoculation of artificially mixed compatible and incompatible tumor cells. Cell Immunol (In Press).

950. Klein, E., Van Furth, R., Johansson, B., Ernberg, I. and Clifford, P.: Immunoglobulin synthesis as cellular marker of malignant lymphoid cells. Proc Cambridge Symp on Oncogenesis and Herpes Type Viruses, 1971 (In Press).

951. Klein, G.: Cambridge Symposium 1971. Summing Up. Proc Cambridge Symp on Oncogenesis and Herpes Type Viruses (In Press).

952. Klein, G.: EBV-associated membrane antigens. Proc Cambridge Symp on Oncogenesis and Herpes Type Viruses, 1971 (In Press).

953. Klein, G.: Tumor immunology. Clin Immunol (In Press).

954. Klein, G., Dombos, L. and Gothoskar, B.: Sensitivity of virogenic and non-virogenic human lymphoblastoid cell lines to superinfection with EB-virus. (In Press).

955. Klein, G. and Harris, H.: Studies on malignant behavior and antigen expression in hybrids derived from the fusion of normal with malignant mouse cells. Proc 1st Int Conf on Cell Differentiation, Nice (R. Harris, ed.) (In Press).

956. Klement, V., Gilden, R.V., Oroszlan, S., Sarma, P., Rongey, R. and Gardner, M.B.: Induction of rat specific C-type RNA virus in Rous virus-induced rat sarcoma cell line (XC) by 5-bromodeoxyuridine. Nature (In Press).

957. Klement, V., Nicolson, M.O., Gardner, M.B., Rongey, R.W., Gilden, R.V. and Huebner, R.J.: Induction of rat species specific type C focus forming RNA virus in cloned non-productive rat cell lines by 5-bromodeoxyuridine. J Natl Cancer Inst (In Press).

958. Kouri, R.E., Lubet, R.A. and Brown, D.J.: Quantitation of aryl hydrocarbon hydroxylase activity in individual hamster fetal cells in vitro. J Natl Cancer Inst (In Press).

959. Kuo, E.Y., Cobb, W.R., Bogden, A.E. and Mason, M.M.: Induction of lactation in non-pregnant rhesus monkeys. Proc 4th Internat Cong Endocrinology (In Press).

960. Lai, M.C. and Duesberg, P.H.: Differences between the envelope glycoproteins and glycopeptides of avian tumor viruses released from transformed and from nontransformed cells. Virology (In Press).

961. Larsen, R.J., Holmes, C.L. and Heath, C.W., Jr.: A statistical test for measuring unimodal clustering. A description of the test and of its application to cases of acute leukemia in metropolitan Atlanta, Georgia. Biometrics (In Press).

962. Lasfargues, E.Y., Coutinho, W.G. and Moore, D.H.: Co-cultivation as a method for the study of human breast carcinomas. Proc 7th Mtg Breast Cancer in Animals and Man, Grenoble, France, June 1972 (In Press).

963. Lasfargues, E.Y., Coutinho, W.G. and Moore, D.H.: Heterotransplantation of a human breast carcinoma cell line. Cancer Res (In Press).

964. Lee, K.M., Nomura, S., Bassin, R.H. and Fischinger, P.J.: Use of an established cat cell line for investigation and quantitation of feline tumor viruses. J Natl Cancer Inst (In Press).

965. Leis, J.P., Berkower, I. and Hurwitz, J.: RNA dependent DNA polymerase activity of RNA tumor viruses. IV. Protein and RNase H associated activity. Proc DNA Synthesis In Vitro, Steenbock Symp., July 1972 (In Press).

966. Leis, J.P. and Hurwitz, J.: Isolation and characterization of an avian myeloblastosis virus stimulatory protein. Proc Natl Acad Sci USA (In Press).

967. Leis, J.P. and Hurwitz, J.: Mechanism of DNA synthesis with avian myeloblastosis virus DNA polymerase. Proc FASEB, Atlantic City, New Jersey, April 1972 (In Press).

968. Leis, J.P. and Hurwitz, J.: Studies of Rauscher and avian viral polymerases. Fed Proc (In Press).

969. Leventhal, B.G., Halterman, R.H., Rosenberg, E.B. and Herberman, R.B.: Immune reactivity of leukemia patients to autologous blast cells. Cancer Res (In Press).

970. Leverage, W.E., Valerio, D.A., Schultz, A.P., Kingsbury, E.W. and Dorey, C.K.: Comparative study on the freeze preservation of spermatozoa. Primate, bovine and human. Lab Anim Sci (In Press).

971. Levine, P.H., Herberman, R.B., Rosenberg, E.B., McClure, P.D., Roland, A., Pienta, R.J. and Ting, R.C.Y.: Acute leukemia in identical twins: search for viral and leukemia associated antigens. J Natl Cancer Inst (In Press).

972. Levine, P.H., O'Conor, G.T. and Berard, C.W.: Antibodies to Epstein-Barr virus (EBV) in American patients with Burkitt's lymphoma. Cancer (In Press).

973. Levine, P.H. and Reisher, J.I.: Studies on the relationship of EBV titers to cell-mediated immunity in patients with Hodgkin's disease. Proc Hodgkin's Disease Symp (In Press).

974. Levine, P.H., Reisher, J.I. and Cho, B.R.: Burkitt's lymphoma - an important entity. Proc 12th Int Cong Med (In Press).

975. Levine, P.H., Stevens, D.A., Coccia, P.F., Dabich, L. and Roland, A.: Infectious mononucleosis prior to acute leukemia: a possible role for the Epstein-Barr virus. Cancer (In Press).

976. Lewandowski, L.J. and Leppla, S.H.: Comparison of the 3' termini of discrete segments of the double-stranded (ds) RNA genomes of cytoplasmic polyhedrosis virus (CPV), wound tumor virus (WTV) and reovirus. J Virol (In Press).

977. Lewandowski, L.J. and Traynor, B.: Comparison of the structure and polypeptide composition of three double-stranded RNA-containing viruses (Diplornaviruses): Cytoplasmic polyhedrosis virus, wound tumor virus and reovirus. J Virol (In Press).

978. Lewis, J., Silber, R., Malathi, V. and Hurwitz, J.: Studies on ligation and transcription of RNA. In: Advances in the Biosciences, Mechanisms and Prospects of Genetic Exchange--Symposium (In Press).

979. Lilly, F.: Antigen expression on spleen cells of Friend virus-infected mice. In: RNA Viruses and Host Genome in Oncogenesis (P. Emmelot and P. Bentvelzen, eds.) (In Press).

980. Lilly, F. and Pincus, T.: Genetic control of murine viral leukemogenesis. Adv Cancer Res (In Press).

981. Lilly, J.R., Anderson, K.D., Hill, J.L., Rosser, S.B. and Randolph, J.G.: Liver transplantation in acute liver failure. J Pediatric Surg (In Press).

982. Lilly, J.R., Tunell, W.P., Anderson, K.D., Hill, J.L., Rosser, S.B., Chandra, R., Altman, R.P. and Randolph, J.G.: Auxiliary liver transplantation: studies on simultaneous portal inflow to both hepatic allograft and native liver. Ann Chir Infant (In Press).

983. Linden, G. and Henderson, B.E.: Genital tract cancers in adolescents and young adults. N Engl J Med (In Press).

984. Livingston, D.M., Parks, W.P. and Scolnick, E.M.: Viral reverse transcriptase in cells transformed by avian tumor viruses. Virology (In Press).

985. Livingston, D.M. and Wacker, W.E.C.: Magnesium metabolism. In: Handbook of Physiology (American Physiology Soc) (In Press).

986. Loeb, W.F., Ablashi, D.V., Armstrong, G.R., Yang, S.S., Valerio, M.G. and Adamson, R.H.: Oncogenicity of herpesvirus saimiri induced lymphoma and the DNA polymerases of the lymphoma derived cell line and H saimiri. Med Primatol (In Press).

987. Long, C., Kelloff, G. and Gilden, R.V.: Variations in sarcoma and leukemia virus activity in somatic cell hybrids. Int J Cancer (In Press)

988. Ludwig, H.O., Biswal, N. and Benyesh-Melnick, M.: Studies on the relatedness of herpesviruses through DNA-DNA hybridization. Virology (In Press).

989. Lytle, C.D., Aaronson, S.A. and Harvey, E.: Host cell reactivation in mammalian cells. II. Survival of herpes simplex virus and vaccinia virus in normal human and xeroderma pigmentosum cells. Int J Radiat Biol (In Press).

990. Magrassi, F. and Tarro, G.: Knowledges reached and in progress on the phenomenons offered by oncogenic viruses. Rec Progr in Med (In Press).

991. Mantyjarvi, R.A.: Presence of virus-specific RNA in hamster cells transformed by simian adenovirus SA7. Arch Ges Virusforsch (In Press).

992. Margolis, S., Oie, H. and Levy, H.B.: The effect of interferon, interferon inducers or interferon-induced viral resistance on subsequent interferon production. J Gen Virol (In Press).

993. Martin, D.P., Darrow, C.C., Valerio, D.A., and Leiseca, S.: Methods of anesthesia in nonhuman primates. Lab Anim Sci (In Press).

994. Martin, D., Leiseca, S.A. and Darrow, C.: Methods of anesthesia in subhuman primates. Anesthesiology (In Press).

995. Maruyama, K.: Studies on human leukemia by membrane immunofluorescence and mixed hemadsorption tests. In: Yearbook of Cancer (In Press).

996. Maruyama, K. and Dmochowski, L.: Studies on cross-species infection of RNA tumor viruses. Proc Texas Med Assoc, May 1972, San Antonio, Texas (In Press).

997. Maruyama, K., Dmochowski, L., Romero, J.J., Wagner, S.H. and Swearingen, G.R.: Studies on human cells infected by leukemia virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

998. Mason, M.M., Bogden, A.S., Ilievski, V., Esber, H.J., Baker, J.R. and Chopra, H.C.: Clinical history of an adenocarcinoma bearing rhesus monkey with a virus resembling oncogenic RNA viruses. J Natl Cancer Inst (In Press).

999. Mayyasi, S.A.: Antilymphocyte serum and lymphoid cell-virus carrier culture: cell kinetics, morphology, EB virus replication, interferon. Cell Immunol (In Press).

1000. McAllister, R.M.: Search for oncogenes in human rhabdomyosarcoma cells. Proc 12th Int Cong Int Assoc Microbiol Soc (In Press).

1001. McAllister, R.M., Nicolson, M., Klement, V., Gardner, M.B., Rasheed, S., Rongey, R.W. Hardy, W.D., Jr., Gilden, R.V. and Huebner, R.J.: Comparison of feline and murine C-type viruses released from RD cells with the RD-114 virus. Nature (In Press).

1002. McBride, C.M., Bowen, J.M. and Dmochowski, L.: Antinucleolar antibodies in sera of melanoma patients. Proc Annu Mtg of The Surgical Forum, San Francisco, California, Oct. 1972 (In Press).

1003. McCain, B., Biswal, N. and Benyesh-Melnick, M.: The subunits of murine sarcoma-leukemia virus RNA. J Gen Virol (In Press).

1004. McCoy, J.L., Herberman, R.B., Rosenberg, E.B., Levine, P.H. and Alford, T.C.: Cellular lymphocyte cytotoxicity reactivity in human leukemia and tissue culture systems. J Natl Cancer Inst (In Press).

1005. McKhann, C.F. and Jagarlamoody, S.M.: Manipulation of the immune response towards immunotherapy of cancer. In: Symp Membranes, Viruses and Immune Mechanisms in Experimental and Clinical Diseases (S.B. Day and R.A. Good, eds.) (In Press).

1006. Meier, H.: Genetic determination of neoplasia and expression of viral genomes in inbred mice. Theoret Appl Genet (In Press).

1007. Meier, H. and Fox, R.R.: Heredity lymphosarcoma in WH rabbits and hereditary m hemolytic anemia associated with thymoma in strain X rabbits. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1008. Meier, H. and Myers, D.D.: Chemical co-carcinogenesis: differential action of various compounds, depression of endogenous C-type RNA genome and influence of different genotypes of mice. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res., Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1009. Melnick, J.L.: Classification and nomenclature of viruses. In: Ultrastructure of Animals, Viruses and Bacteriophages--An Atlas (A.J. Dalton and F. Haguenau, eds.), Academic Press, New York, New York (In Press).

1010. Melnick, J.L. (ed.): Proc 2nd Int Cong Virol, Budapest, Hungary, 1971, S. Karger, Basel, Switzerland (In Press).

1011. Miller, M.F., Allen, P.T., Bowen, J.M., Dmochowski, L., Hixson, D.C. and Williams, W.C.: Particle counting of partially purified RNA tumor viruses by a thin sectioning technique. Proc 30th Annu Mtg Electron Microscopy Society of America, Los Angeles, California, August 1972 (In Press).

1012. Milo, G.E., Schaller, J.P. and Yohn, D.S.: Hormonal modification of adenovirus transformation of hamster cells in vitro. Cancer Res (In Press).

1013. Mittal, K.K. and Terasaki, P.I.: Cross-reactivity in the HL-A system. In: Tissue Antigens (In Press).

1014. Miyajima, T., Hirato, A.A. and Terasaki, P.I.: Escape from sensitization to HL-A antibodies. Transplantation (In Press).

1015. Munoz, N. and Matko, I.: Histological types of gastric cancer and its relationship with intestinal metaplasia. Cancer Res (In Press).

1016. Murphy, W.H. and Bullis, C.: Antigenic diversity of strains of mycoplasma fermentans. J Gen Microbiol (In Press).

1017. Naegele, R.F. and Granoff, A.: Viruses and renal carcinoma of Rana pipiens. XIII. Transmission of the Lucke tumor by herpesvirus-containing ascitic fluid from a tumor-bearing frog. J Natl Cancer Inst (In Press).

1018. Neauport-Sautes, D., Silvestre, D., Lilly, F. and Kourlisku, F.M.: Molecular independence of H-2K and H-2D antigens on the cell surface. Proc Transplantation Society Congress, Sept. 1972 (In Press).

1019. Nelson-Rees, W.A., Hooser, L.E. and Hackett, A.J.: Chronic poliovirus infection of co-cultivated monkey cells (CMMT) harboring the Mason-Pfizer monkey virus (M-PMV). J Natl Cancer Inst (In Press).

1020. Nelson-Rees, W.A., Hooser, L.E. and Hackett, A.J.: Resistance to poliovirus (type 1) by rhesus monkey cells which are producing the Mason-Pfizer monkey virus. Proc 10th Annu Conf Somatic Cell Genetics (In Press).

1021. Nelson-Rees, W.A. and Scher, C.D.: Chromosomes of virus transformed BALB/c3T3 cells. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1022. Newton, W.A., Jr., Allen, P.T., East, J.L., Maruyama, K., Bowen, J.M., Georgiades, J., Priori, E.S. and Dmochowski, L.: Molecular studies of cells derived from human solid tumors. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, March 1972, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

1023. Nicolson, M.O. and McAllister, R.M.: Infectivity of human adenovirus-1 DNA. Virology (In Press).

1024. Nomura, S., Fischinger, P.J., Mattern, C.F.T., Peebles, P.T., Bassin, R.H. and Friedman, G.P.: Revertants of mouse cells transformed by murine sarcoma virus. I. Characterization of flat and transformed sublines without a rescuable murine sarcoma virus. Virology (In Press).

1025. Nonoyama, M. and Pagano, J.S.: Separation of Epstein-Barr virus DNA from large chromosomal DNA in non-virus-producing cells. Nature (In Press).

1026. Oettgen, H.F. and Hellstrom, K.E.: Tumor immunology. In: Cancer Medicine (E. Frei and J. Holland, eds.) (In Press).

1027. Oldham, R.K., McCoy, J.L. and Herberman, R.B.: Evaluation of a cell-mediated cytotoxicity assay utilizing 125-I-iododeoxyuridine labeled tissue culture target cells. J Natl Cancer Inst (In Press).

1028. Olpin, J.L. and Burger, C.L.: Analytical measurements of isopycnic density in the preparative ultracentrifuge with application to FeLV and FeLV-RNA. Anal Biochem (In Press).

1029. Olsen, R.G. and Yohn, D.S.: Demonstration of antibody in cat sera to feline oncornavirus by complement-fixation inhibition. J Natl Cancer Inst (In Press).

1030. Omine, M. and Perry, S.: Use of cell separation at 1g for cytokinetic studies in spontaneous AKR leukemia. J Natl Cancer Inst (In Press).

1031. Oroszlan, S., Bova, D., Toni, R. and Gilden, R.V.: Antibodies to the group specific antigens of mammalian C-type viruses: interaction of IgM and IgG containing serum fractions for detection of cross-reactive antigenic determinants. Science (In Press).

1032. Ortiz de Landazuri, M. and Herberman, R.B.: Immune response to Gross virus-induced lymphoma. III. Characteristics of the cellular immune response. J Natl Cancer Inst (In Press).

1033. Ortiz de Landazuri, M. and Herberman, R.B.: In vitro activation of cellular immune response to Gross virus-induced lymphoma. J Exp Med (In Press).

1034. Oshiro, L.S., Riggs, J.L., Taylor, D.O.N. and Lennette, E.H.: Replication of feline C-type virus at the plasma membrane of erythrocytes of cats with myeloproliferative disorders. J Natl Cancer Inst (In Press).

1035. Owens, R.B.: Tissue culture studies of mouse mammary tumor cells and associated viruses. J Natl Cancer Inst (In Press).

1036. Oxman, M.N., Takemoto, K.K. and Eckhart, W.: Polyoma T antigen synthesis by temperature sensitive mutants of polyoma virus. Virology (In Press).

1037. Palmer, W.G.: Affinity chromatography: interactions between sepharose-linked and soluble gamma globulins. Biochem Biophys Acta (In Press).

1038. Palmer, W.G. and Holleman, J.W.: Literature survey. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press)

1039. Papageorgiou, P.S. and Glade, P.R.: Progress in lymphology: in vitro studies of lymphocytes. Lymphology (In Press).

1040. Papageorgiou, P.S., Henley, W.L. and Glade, P.R.: Production and characterization of migration inhibitory factor(s) (MIF) of established lymphoid and non-lymphoid cell lines. J Immunol (In Press).

1041. Parks, W., Gillette, R.W., Blackman, K., Verna, J.E. and Sibal, L.R.: Mammary tumor virus expression in mice: immunological studies. Proc 7th Mtg on Breast Cancer in Animals and Man, Grenoble, France, June 1972 (In Press).

1042. Parks, W.P., Scolnick, E.M. and Livingston, D.M.: Radioimmunoassay of type C viral proteins. J Immunol (In Press).

1043. Pattillo, R.A.: Production of hormones and intercellular substances. In: Methods and Applications of Tissue Culture (Kruse and Patterson, eds.), Academic Press, New York, New York (In Press).

1044. Pattillo, R.A.: Trophoblastic cancers: chorionic gonadotropin hormone production, antigenic expression, and trophoblast re-differentiation in multiple forms of malignancy. In: Pathobiology Annual (In Press).

1045. Pattillo, R.A., Story, M.T., Hershman, J.M., Delfs, E. and Mattingly, R.F.: Hormone control of differentiation and embryonic antigens in human placental tumor cells in vitro. Proc 2nd Conf on Embryonic and Fetal Antigens in Cancer, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, eds.) (In Press).

1046. Pearson, G., Orr, T., Redmon, L. and Bergs, V.V.: Membrane immunofluorescence studies on cells producing rat C-type virus particles. Int J Cancer (In Press).

1047. Pearson, L.D. and Snyder, S.P.: A method of bandaging queens to prevent nursing by newborn kittens until blood samples are collected. Lab Anim Sci (In Press).

1048. Perry, S.: Cancer chemotherapy present status and direction. D.O. (Amer Osteopathic Assoc) (In Press).

1049. Perryman, L.E., Hoover, E.A. and Yohn, D.S.: Immunological reactivity of the cat: immunosuppression in experimental feline leukemia. J Natl Cancer Inst (In Press).

1050. Person, D.A., Brunschwig, J.P., Hall, W.T., Sinha, A.K., Pathak, S., Sharp, J.T. and Rawls, W.E.: A latent C-type virus in Chinese hamster ovary cells. In Vitro (In Press).

1051. Pienta, R.J., Fine, D.L., Hurt, T., Smith, C.K., Landon, J.C. and Chopra, H.C.: In vitro transformation of rhesus foreskin cells by Mason-Pfizer monkey virus (M-PMV). J Natl Cancer Inst (In Press).

1052. Piessens, W.F., Schur, P.H., Moloney, W.C. and Churchill, W.H.: Lymphocyte surface immunoglobulins in lymphoproliferative diseases. Clin Res (In Press).

1053. Plata, E.J. and Murphy, W.H.: Growth and hematologic properties of Balb/WM strain of inbred mice. Lab Anim Sci (In Press).

1054. Portugal, F.H.: Elution profiles of lysine and tyrosine transfer RNA during avian development. Mech of Agina and Develop. (In Press).

1055. Portugal, F.H.: Specificity of lysine and tyrosine transfer RNA fractions for RNA codons. Mech of Aging and Develop. (In Press).

1056. Priori, E.S., Dmochowski, L., Myers, B., Shigematsu, T. and Wilbur, J.R.: A type C virus-producing human cell culture (ESP-1). In: Unifying Concepts of Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1057. Priori, E.S., Dmochowski, L., Wilbur, J.R., Myers, B. and Shigematsu, T.: A type C virus-producing culture of human origin. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1058. Priori, E.S., Shigematsu, T., Myers, B. and Dmochowski, L.: Spontaneous production of type C virus particles of a culture derived from rat embryo cells. Proc 30th Annu Mtg of the Electron Microscopy Society of America, Los Angeles, Calif., Aug. 1972 (In Press).

1059. Proffitt, M.R., Congdon, C.C. and Tyndall, R.L.: The combined action of Rauscher leukemia virus and lactic dehydrogenase virus on mouse lymphatic tissue. Int J Cancer (In Press).

1060. Purtilo, D., Kersey, J.H., Mallgren, H. and Yunis, E.: Alpha fetoprotein: clinical use and biologic implications. Am J Clin Pathol (In Press).

1061. Rabin, H.: Studies on oncogenic viruses of primate origin. Am J Phys Anthropol (In Press)

1062. Rabin, H., Griesemer, R., Theilen, G.H. and Fine, D.L.: Virus isolations from spontaneous rhesus monkey lymphosarcomas. Proc 3rd Conf on Exp Med and Surg in Primates, Lyon, France, June 1972, S. Karger, New York (In Press).

1063. Rabin, H., Nelson, V.G., Theilen, G.H., Espana, C. and Smith, E.K.: Rhesus monkey lymphoma: study of one case. Med Primatol (In Press).

1064. Rabin, H., Theilen, G.H., Dungworth, D.L., Sarma, P.S., Nelson-Rees, W.A. and Cooper, R.W.: Continuing studies of feline sarcoma virus induced tumors in nonhuman primates. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1065. Rabin, H., Theilen, G.H., Sarma, P.S., Dungworth, D.L., Nelson-Rees, W.A. and Cooper, R.W.: Tumor induction in squirrel monkeys by the ST-strain of feline sarcoma virus. J Natl Cancer Inst (In Press).

1066. Rangan, S.R.S., Wong, M.C., Moyer, P.P. and Jensen, E.M.: Cytopathogenic test for feline leukemia virus infections. Appl Microbiol (In Press).

1067. Rapp, F.: The PARA-adenoviruses. In: Progress in Experimental Tumor Research, Vol. 16: Oncogenic Viruses (In Press).

1068. Rapp, F., Conner, R., Glaser, R. and Duff, R.: Absence of leukosis virus markers in hamster cells transformed by herpes simplex virus type 2. J Virol (In Press).

1069. Rapp, F. and Duff, R.: Transformation of hamster cells after infection by inactivated herpes simplex virus type 2. Proc Symp Oncogenesis and Herpes-Type Viruses, Cambridge, England, June 1972 (In Press).

1070. Raskas, H.J. and Green, M.: DNA-RNA and DNA-DNA hybridization in virus research. In: Methods in Virology, Vol. 5, Academic Press, New York (In Press).

1071. Rawls, W.E., Adam, E., Smith, J.W. and Melnick, J.L.: Antibodies to herpesvirus types 1 and 2 and cervical cancer. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., June 1972 (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

1072. Rein, A. and Smith, H.S.: Partial immunity of SV40 "cryptic transformants" to cells re-transformated by SV40. Proc 23rd Annu Mtg of the Tissue Culture Assoc (In Press).

1073. Remold, H.G. and David, J.R.: Studies on migration inhibitory factor from concanavalin-A stimulated lymphoid cells. Proc 6th Leukocyte Culture Conf (In Press).

1074. Rhim, J.S., Cho, H.Y., Rabstein, L., Gordon, R.J., Bryan, R.J., Gardner, M.B. and Huebner, R.J.: Transformation induced by extracts of city smog in mouse cells infected with AKR leukemia virus. Nature (In Press).

1075. Rhim, J.S., Huebner, R.J., Takemoto, K.K. and Gilden, R.V.: In vitro carcinogenesis studies: dual effects of RNA tumor viruses and carcinogenic chemicals or DNA viruses. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1076. Rickard, C.G., Post, J.E., Noronha, F. and Barr, L.M.:. Interspecies infection by feline leukemia virus: serial cell-free transmission in dogs of malignant lymphomas induced by feline leukemia virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1077. Rodriguez, A.R., Kalter, S.S., Helmke, R.J. and Heberling, R.L.: Viral infections of the Kenya baboon (Papio cynocephalus) in its natural habitat. Primates (In Press).

1078. Rosenberg, E.B., Herberman, R.B., Levine, P.H., Wunderlich, J.R., Halterman, R.H. and Mc Coy, J.L.: Detection of leukemia associated antigens in identical twins. Proc Amer Fed Clin Res (In Press).

1079. Ross, J., Tronick, S., Scolnick, E.M.: Polyadenylate rich RNA in the 70S RNA of murine leukemia-sarcoma virus. Virology (In Press).

1080. Rubin, D.J.: Immunogenicity of EL4 in C57BL/6 mice demonstrated by intradermal immunization. Proc Conf on Immunology of Carcinogenesis, Gatlinburg, Tennessee, May 1972. In: Natl Cancer Inst Monograph (In Press).

1081. Sacksteder, M.R., Kasza, L., Palmer, J.L. and Warren, J.: Leukemia in conventional and germfree Fischer rats. In: Proc 4th Int Symp, Acadmeic Press, New York (In Press).

1082. Salerno, R.A., Whitmire, C.E., Garcia, I.M. and Huebner, R.J.: Chemical carcinogenesis in mice inhibited by interferon. Nature (In Press).

1083. Salinas, F.A., Smith, J.A. and Hanna, M.G., Jr.: Modification of the spleen colony-forming assay to demonstrate immunologic cross-reactivity of antigens common to tumor and fetal cells. In: Embryonic and Fetal Antigens in Cancer, Vol. 2, AEC Symp Series, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, eds.) (In Press).

1084. Salzberg, S. and Green, M.: Surface alterations of cells carrying RNA tumor virus genetic information. Nature (In Press).

1085. Santos, G.W., Williams, G.M., Bias, W.B., Anderson, P.N., Gratziano, K.D., Klein, D.L. and Burke, P.J.: Immunological studies in acute leukemia. J Natl Cancer Inst (In Press).

1086. Sarkar, N.H. and Moore, D.H.: Electron microscopy in mammary cancer research. J Natl Cancer Inst (In Press).

1087. Sarkar, N.H. and Moore, D.H.: On the possibility of a human breast cancer virus. Nature (In Press).

1088. Sarkar, N., Moore, D., Kramarsky, B. and Chopra, H.C.: The mammary tumor virus. In: Ultrastructure of Animal Viruses and Bacteriophages--An Atlas (A.J. Dalton and F. Haguenau, eds.), Academic Press, New York (In Press).

1089. Sarma, P.S., Gazdar, A.F., Turner, H.C. and Dejkunchorn, P.D.: Gazdar strain of murine sarcoma virus. Biological and antigenic interaction with the heterologous hamster host. Proc Soc Exp Biol Med (In Press).

1090. Sarma, P.S., Kabigtin, A. and McDonough, S.: The SM strain of feline sarcoma virus biologic and antigenic characteristics of virus. Proc Soc Exp Biol Med (In Press).

1091. Sarma, P.S. and Log, T.: Viral envelope antigens of feline leukemia and sarcoma virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1092. Schneider, R.: Feline malignant lymphoma: environmental factors and the occurrence of this viral cancer in cats. Int J Cancer (In Press).

1093. Schneider, R.: Human cancer in households containing cats with malignant lymphoma. Int J Cancer (In Press).

1094. Schlom, J. and Spiegelman, S.: Biochemical characterization of virus particles in mouse and human milk. Institut National de la Recherche Medicale (In Press).

1095. Scolnick, E.M.: RNA-dependent DNA polymerases in mammalian cells. Dev Biol (In Press).

1096. Scolnick, E.M.: RNA-dependent DNA polymerases of RNA-containing viruses. In: Current Topics in Biochemistry, Academic Press, New York (In Press).

1097. Scolnick, E.M., Parks, W.P. and Livingston, D.M.: Radioimmunoassay of mammalian type C virion polypeptides. I. Species specific reactions of murine and feline viruses. J Immunol (In Press).

1098. Scolnick, E.M., Parks, W.P. and Livingston, D.M.: Radioimmunoassay of type C viral proteins. J Immunol (In Press).

1099. Scolnick, E.M., Parks, W.P. and Todaro, G.J.: The reverse transcriptase of primate viruses as immunological markers. Science (In Press).

1100. Scolnick, E.M., Parks, W.P. and Todaro, G.J.: Reverse transcriptase as immunological markers for primate C-type viruses. Science (In Press).

1101. Scott, W.A., Shields, R. and Tomkins, G.M.: Mechanism of hormonal induction of tyrosine aminotransferase studied by measuring the concentration of growing enzyme molecules. Proc Natl Acad Sci (In Press).

1102. Seman, G. and Dmochowski, L.: Synthesis of virus particles in reproductive organs of male mice of different strains. J Natl Cancer Inst (In Press).

1103. Shanmugam, G. and Green, M.: Comparison of the polypeptide composition of several RNA tumor viruses. Virology (In Press).

1104. Shanmugam, G., Vecchio, G., Attardi, D. and Green, M.: Immunological studies on viral polypeptide synthesis in cells replicating murine sarcoma-leukemia virus. J Virol (In Press).

1105. Shevach, E.M., Herberman, R., Frank, M.M. and Green, I.: Receptors for complement and immunoglobulin on human leukemic cells and human lymphoblastoid cell lines. J Clin Invest (In Press).

1106. Shifrine, M., Wolf, H.G., Taylor, N.J., Galligan, S.J., Wilson, F.D., Colgrove, G.S. and Bustad, L.K.: Transplantation of radiation-induced canine myelomonocytic leukemia. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1107. Shigematsu, T. and Dmochowski, L.: Studies on the acid mucopolysaccharide coat of viruses and transformed cells. Cancer (In Press).

1108. Sigel, M.M., Meyers, P. and Holden, H.T.: Homologous and heterologous immunization against Rous sarcoma. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1109. Simkovic, D.: Characteristics of tumours induced in mammals, expecially rodents, by viruses of the avian sarcoma leukosis group (ASLV). Advances in Virus Res, Academic Press, Inc., New York (In Press).

1110. Sinkovics, J.G.: Chairman's Introduction: search for human tumor viruses. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas, March 1972 (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

1111. Sinkovics, J.G.: Monitoring in vitro of cell-mediated immune reactions to tumors. In: Methods of Cancer Research, Vol. 7 (H. Busch, ed.) (In Press).

1112. Sinkovics, J.G., Ahmed, N., Hrgovcic, M.J., Cabiness, J.R. and Wilbur, J.R.: Cytotoxic lymphocytes. II. Antagonism and synergism between serum factors and lymphocytes of patients with sarcomas as tested against cultured tumor cells. Texas Rep Biol Med (In Press).

1113. Sinkovics, J.G., Cabiness, J.R. and Shullenberger, C.C.: Disappearance after chemotherapy of blocking serum factors as measured in vitro with lymphocytes cytotoxic to tumor cells. Cancer (In Press).

1114. Sinkovics, J.G., Cabiness, J.R. and Shullenberger, C.C.: In vitro cytotoxicity of lymphocytes to human sarcoma cells. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1115. Sinkovics, J.G. and Gyorkey, F.: Hodgkin's disease:the involvement of viral agents in the etiology. Hematol Rev (In Press).

1116. Sinkovics, J.G., Reeves, W.J. and Cabiness, J.R.: Reactions of leukocytes and sera of patients with cultured tumor cells. In: Conference on Virus Tumorigenesis and Immunogenesis. (W.S. Ceglowski and H. Friedman, eds.), Academic Press, New York, New York, 1972 (In Press).

1117. Sinkovics, J.G., Sullivan, M.P. and Wilbur, J.R.: Disappearance of blocking serum factors in patients receiving chemotherapy for disseminated rhabdomyosarcoma. Proc Annu Mtg Amer Soc Oncology, May 1972 (In Press).

1118. Sinkovics, J.G., Tebbi, K. and Cabiness, J.R.: Cytotoxicity of lymphocytes to established cultures of human tumors: evidences for specificity. J Natl Cancer Inst (In Press).

1119. Skurzak, K., Klein, E., Yoshida, T. and Lamon, E.: Concentration-dependent influence of immune sera on the cytotoxic effect of lymphocytes in the MSV rat system. J Exp Med (In Press).

1120. Smith, J.W., Adam, E., Melnick, J.L. and Rawls, W.E.: Use of the 51CR release test to demonstrate patterns of antibody response in humans to herpesvirus types 1 and 2. J Immunol (In Press).

1121. Snyder, S.P., Dungworth, D.L., Kawakami, T.G., Callaway, E.E. and Lau, D.T.L.: Two cases of lymphosarcoma in gibbons with associated C-type virus. J Natl Cancer Inst (In Press).

1122. Spiegelman, S., Axel, R. and Schlom, J.: Viral-related RNA in human and mouse mammary tumors. J Natl Cancer Inst (In Press).

1123. Spiegelman, S., Schlom, J., Axel, R., Hehlmann, R. and Kufe, D.: Molecular probing for a viral etiology of human cancer. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas, March 1972 (J. Bowen, ed.) Williams and Wilkins, Baltimore, Maryland (In Press).

1124. Stanbridge, E.J., Perkins, F.T. and Hayflick, L.: Cell tumorigenicity detected by heterotransplantation into mice immunosuppressed with anti-lymphocytic serum. In: Immunobiological Standardization, S. Karger, Basel, Switzerland (In Press).

1125. Stephenson, J.R. and Aaronson, S.A.: A genetic locus for inducibility of C-type virus in Balb/c cells: the effect of a nonlinked regulatory gene on detection of virus after chemical activation. Proc Natl Acad Sci USA (In Press).

1126. Stevens, D.A., O'Conor, G.T., Levine, P.H. and Rosen, R.B.: Acute leukemia with Burkitt lymphoma cells (a new entity) and Burkitt's lymphoma: simultaneous onset in American siblings. Ann Intern Med (In Press).

1127. Storb, R., Kolb, H.J., Graham, T.C., Ochs, H.D. and Thomas, E.D.: Principles of marrow grafting derived from canine studies. Exp Hemat (In Press).

1128. Strouk, V., Grundner, G., Fenyo, E.M. Lamon, E., Skurzak, H. and Klein, G.: Lack of distinctive surface antigen on cells transformed by murine sarcoma virus. J Exp Med (In Press).

1129. Sverak, L., Steele, R.W., Bellanti, J.A. and Heine, U.I.: RNA directed RNA polymerase in cell lines derived from human epithelial carcinoma. Science (In Press).

1130. Szakacs, J. and Cordrey, L.J.: Benign giant cell tumor of bone with subcutaneous recurrence. J Bone Joint Surg (Br.) (In Press).

1131. Takasugi, M., Mickey, M.R. and Terasaki, P.I.: Quantitation of the microassay for cell-mediated immunity through electronic image analysis. In: Natl Cancer Inst Monograph (In Press).

1132. Takasugi, M. and Terasaki, P.I.: Detection of HL-A and other cell surface antigens on cultured cells by a cytotoxic plating inhibition test. J Natl Cancer Inst (In Press).

1133. Takasugi, M., Ward, P.H., Mickey, M.R. and Terasaki, P.I.: Allogeneic cell-mediated testing for human tumor antigens. In: Natl Cancer Inst Monograph (In Press).

1134. Tarro, G.: Type-specificity of nonvirion complement fixing antigens produced by human herpesviruses. Proc Natl Acad Sci USA (In Press).

plaques in different cell lines by the use of gammaglobulin. Giorn Batteriol Virol Immunol (In Press).

1136. Tarro, G., Battista, A., Gattoni, S. and Mazzuca, A.: Optimum procedures for producing stable herpes simplex virus stocks and methods for determining them. Giorn Mal Infect Parassit (In Press).

1137. Tatsis, B., Dosik, H., Rieder, R.F. and Lee, S.: Hemoglobin hasharon: severe hemolytic anemia and hypersplenism associated with a slightly unstable hemoglobin. Proc 4th Conf Clin Delineation of Birth Defects (In Press).

1138. Taylor, B.A.: Recombinant inbred lines: a new approach in genetic analysis. Theoret Appl Genet (In Press).

1139. Tennant, R.W.: Requirement of specific cellular synthesis for the replication of Kilham rat virus, H-1 virus and minute virus of mice. Proc 2nd Cong Virol June-July, 1971, Budapest, Hungary (In Press).

1140. Terasaki, P.I., Stiehm, E.E., Miyajima, T. and Sengar, D.P.S.: Extraneous lymphocytic HL-A antigens in severe combined immunodeficiency disease. Transplantation (In Press).

1141. Tevethia, S.S.: Diversity of the immune response of tumor-bearing hosts to tumor-specific transplantation antigen. Proc Symp Viral Tumorigenesis and Immunogenesis, University Park, Pennsylvania (In Press).

1142. Tevethia, S.S. and Zarling, J.M.: Participation of macropahges in tumor immunity. In: Natl Cancer Inst Monograph: Proc Conf on Immunology of Carcinogenesis (In Press)

1143. Theilen, G.H., Rabin, H., Gould, D., Fowler, M.E., Cooper, R.W. and Dungworth, D.L.: Biological studies on a C-type virus present in tissues of a woolly monkey (Lagothrix spp.) with fibrosarcoma. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1144. Theilen, G.H., Wolfe, L.G., Rabin, H., Deinhardt, F., Dungworth, D.L. and Cooper, R.W.: Biological studies in four species of nonhuman primates with simian sarcoma virus (Lagothrix). In: Unifying Concepts of Leukemia, Bibl Haematol, 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1145. Ting, C.C., Lavrin, D.H. and Herberman, R.B.: Antibodies to fetal antigens. In: Embryonic and Fetal Antigens in Cancer, Vol. 2, AEC Symp Series, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, Jr., eds.) (In Press).

1146. Ting, C.C., Lavrin, D.H., Shiu, G. and Herberman, R.B.: Expression of fetal antigens in tumor cells and their relationship to tumor specific antigens of papova virus-induced tumors. Proc Natl Acad Sci USA (In Press).

1147. Todaro, G.J.: Detection and characterization of RNA tumor viruses in normal and transformed cells. In: Perspectives in Virology (M. Pollard, ed.) Academic Press, Inc., New York (In Press).

1148. Todaro, G.J.: Reverse transcriptases of RNA tumor viruses. Proc Int Cancer Conf, March 1972, Sydney, Australia (In Press).

1149. Todaro, G.J., Aaronson, S.A., Scolnick, E.M., Ross, J. and Parks, W.P.: Reverse transcriptases of RNA tumor viruses: immunological relationships. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1150. Todaro, G.J. and Huebner, R.J.: Virogenes and oncogenes: evidence to support their existence. Proc Natl Acad Sci USA (In Press).

1151. Tomkins, G.M., Levinson, B.B., Baxter, J.D. and Dethlefsen, L.: Further evidence for posttranscriptional control of inducible tyrosine aminotransferase synthesis in cultured hepatoma cells. Nature (In Press).

1152. Toplisky, M., Siltzbach, L.E., Williams, M. and Glade, P.R.: Lymphocyte response in sarcoidosis. Lancet (In Press).

1153. Tsuchida, N., Robin, M.S. and Green, M.: Viral RNA subunits in cells transformed by RNA tumor viruses. Science (In Press).

1154. Tyndall, R.L., Otten, J. and Estes, P.C.: Some responses of mice to the presence of fetal and leukemic tissues. In: Embryonic and Fetal Antigens in Cancer, Vol. 2, AEC Symp Series, Oak Ridge, Tenn., Feb. 1972 (N.G. Anderson and J.H. Coggin, eds.) (In Press).

1155. Varmus, H.E., Bishop, J.M., Nowinski, R. and Sarkar, N.: Detection of mammary tumor virus specific nucleotide sequences in the DNA of high and low incidence mouse strains. Nature (New Biol) (In Press).

1156. Vaughn, G.L., Tennant, R.W. and Cook, J.S.: Increase in surface binding sites in RNA virus transformed mammalian cells. Proc Am Soc Cell Biol (In Press).

1157. Viola, M.V.: 70S RNA and reverse transcriptase in a long term human cell line. Nature (New Biol) (In Press).

1158. Vogt, P.K., Wyke, J.A., Weiss, R.A., Friis, R.R., Katz, E. and Linial, M.: Avian RNA tumor viruses: mutants, markers and genotypic mixing. In: Molecular Studies in Viral Neoplasia, Proc 25th Annu Symp Fund Cancer Res, Univ. of Texas, M.D. Anderson Hosp and Tumor Inst, Houston, Texas, March 1972 (J. Bowen, ed.), Williams and Wilkins, Baltimore, Maryland (In Press).

1159. Von der Helm, K.: The replication of RNA tumor viruses. In: Int Symp on Recent Results in Cancer Research, Dusseldorf, West Germany (In Press).

1160. Wallis, C. and Melnick, J.L.: Detection of protein contaminants in biological preparations by discontinuous counterimmunoelectrophoresis. Infec Immun (In Press).

1161. Waters, L.C. and Yang, W.K.: Comparative biochemical properties of the RNA-directed DNA polymerases from Rauscher murine leukemia virus and avian myeloblastosis virus. Biochemistry (In Press).

1162. Wedum, A.G., Barkley, W.E. and Hellman, A: Handling of infectious agents. Am Vet Med Assoc (In Press).

1163. Whitmire, C.E., Salerno, R.A., Merold, V.A. and Rabstein, L.S.: The effects of age at treatment and dose of 3-methylcholanthrene on the development of leukemia and sarcomas in AKR mice. J Natl Cancer Inst (In Press).

1164. Whitmire, C.E., Salerno, R.A. and Rabstein, L.S.: Effect of thymectomy, splenectomy and 3-methylocholanthrene on neoplasia expression, incidence and latency in AKR mice. Proc Soc Exp Biol Med (In Press).

1165. Whitmire, C.E., Salerno, R.A., Rabstein, L.S. and Huebner, R.J.: RNA tumor virus antigen expression in chemically-induced tumors. Significance of specific chemical carcinogens to the depression of the C-type RNA virogene and oncogene expressions. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971, (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1166. Whitmire, C.E., Salerno, R.A., Rabstein, L.S., Huebner, R.J. and Turner, H.C.: RNA tumor-virus antigen expression in chemically induced tumors. Virus-genome-specified common antigens detected by complement fixation in mouse tumors induced by 3-methylcholanthrene. In: Immunology and Medicine (R. Acton, ed.) (In Press).

1167. Wigzell, H., Golstein, P., Svedmyr, E.A.J. and Jondal, M.: Impact of fractionation procedures on lymphocyte activities in vitro and in vivo. Separation of cells with high concentrations of surface immunoglobulin. Transplant Proc (In Press).

1168. Wittliff, J.L. and Kenney, F.T.: Regulation of yolk protein synthesis in amphibian liver. I. Induction of lipovitellin synthesis by estrogen. Biochim Biophys Acta (In Press).

1169. Wittliff, J.L., Lee, K.L. and Kenney, F.T.: Regulation of yolk protein synthesis in amphibian liver. II. Elevation of ribonucleic acid synthesis by estrogen. Biochim Biophys Acta (In Press).

1170. Wolfe, L.G. and Deinhardt, F.: Oncornaviruses associated with spontaneous and experimentally-induced neoplasia in nonhuman primates: a review. Proc 3rd Conf on Exptl Med and Surg in Primates, Lyon, France, June 1972 (In Press).

1171. Wolfe, L., Ogden, J., Deinhardt, J., Fisher, L. and Deinhardt, F.: Breeding and hand-rearing marmosets for viral oncogenesis studies. Proc Symp of Breeding Nonhuman Primates for Laboratory Use, Berne, Switzerland, June 1971 (In Press).

1172. Wolfe, L.G., Smith, R.D., Hoekstra, J., Marczynska, B., Smith, R.K., McDonald, R., Northrop, R.L. and Deinhardt, F.: Oncogenicity of feline fibrosarcoma viruses in marmoset monkeys: pathologic virologic and immunologic findings. J Natl Cancer Inst (In Press).

1173. Wright, W. and Hayflick, L.: Formation of anucleate and multinucleate cells in normal and SV40 transformed WI-38 by cytochalasin B. Exp Cell Res (In Press).

1174. Wu, A.M., Ting, R.C., Yang, S.S., Gallo, R.C. and Paran, M.: RNA tumor virus and reverse transcriptase. I. Biochemical studies on the ESP-1 particles. II. Role of the reverse transcriptase in murine RNA tumor virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp of Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1175. Yang, S.S., Herera, F., Smith, G., Reitz, M., Ting, R.C. and Gallo, R.C.: Rifamycin antibiotics: some potent and selective inhibitors of Rauscher (murine) leukemia virus reverse transcriptase and of purified DNA polymerases from human normal and leukemic lymphoblasts. J Natl Cancer Inst (In Press).

1176. Yang, W.K., Snodgrass, M.J. and Waters, L.C.: Search for RNA-directed DNA polymerase in intracisternal "A" particles of mouse plasma cell tumors. J Natl Cancer Inst (In Press).

1177. Yohn, D.S.: Sex-related resistance in hamsters to adenovirus oncogenesis. Prog Exp Tumor Res (In Press).

1178. Yohn, D.S. and Olsen, R.G.: Antibodies to the mammalian oncornavirus interspecies antigen (gs-3) in feline sera. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1179. Zamecnik, P.C.: Minor base changes in transfer RNA in avian myeloblastosis virus. In: Unifying Concepts of Leukemia, Bibl Haematol 39, Proc 5th Int Symp on Comparative Leukemia Res, Padova, Italy, Sept. 1971 (R.M. Dutcher and L. Chieco-Bianchi, eds.), S. Karger, Basel, Switzerland, 1972 (In Press).

1180. Zarling, J.M. and Tevethia, S.S.: Transplantation immunity to SV40-transformed cells in tumor-bearing mice. I. Development of cellular immunity to SV40 TSTA during tumorigenesis by transplanted cells. J Natl Cancer Inst (In Press).

1181. Zarling, J.M. and Tevethia, S.S.: Transplantation immunity to SV40-transformed cells in tumor bearing mice. II. Evidence for macrophage participation at the effector level of tumor cell rejection. J Natl Cancer Inst (In Press).

1182. Zbar, B., Bernstein, I.D., Bartlett, G.L., Hanna, M.G., Jr. and Rapp, H.J.: Immunotherapy of cancer: Regression of intradermal tumors and prevention of growth of lymph node metastases after intralesional injection of living mycobacterium bovis (BCG). J Natl Cancer Inst (In Press).

1183. Zimmerman, E.M., Freeman, A.E., Price, P.J., Holbrook, Z. and Uhlendorf, C.P.: A simple interferon assay as an adjunct for determining genus of cell cultures. In Vitro (In Press).

1184. Burger, M.M.: Surface changes in transformed cells detected by lectins. Fed Proc (In Press).

1185. Burger, M.M.: Neuroscience research program workshop on membranes, Boston, 1972 (In Press).

1186. Burger, M.M.: Mitotic cell surface changes. ICN-UCLA Symposium on Biological Membranes, Catalina, 1972 (C.F. Fox, ed.) (In Press).

1187. Burger, M.M.: Role of the cell surface in growth and transformation. 30th Symp of Soc of Developmental Biology, Seattle, 1971, VII, (F. Skoog, ed.), Academic Press (In Press).

1188. Burger, M.M.: Cell-cell interactions. Hoppe-Seyler's Phyziological Chemistry: 353, 497, 1972 (abstract).

1189. Burger, M.M., Bombik, B.M. and Noonan, K.D.: Cell surface alterations in transformed tissue culture cells and their possible significance in growth control. Psoriasis Workshop, NIH, Bethesda, October 1971 (In Press).

1190. Burger, M.M. and Noonan, K.D.: Cell surface alterations in transformed cells as monitored by plant agglutinins. Proc 1st Int Conf on Cell Differentiation, Nice, Sept. 1971 (In Press).

1191. Burger, M.M. and Noonan, K.D.: Surfacee membrane alterations and relevance to cell-cell interactions and growth control in tissue culture. Mosbach Colloquium. 1972 (In Press).

1192. Chesterman, F.C., Harvey, J.J., Branca, M., Phillips, D.E.H., Hallowes, R.C. and Bassin, R.H.: Tumors and other lesions induced by murine sarcoma viruses. In: Prog Exper Tumor Res 16, (F. Homberger, ed.), S. Karger, New York, 1972.

1193. Fischinger, P.J., Lange, J. and Schafer, W.: Activating and protective capacities of a purified electrophoretic fraction of murine leukemia virus for murine leukemia virus infectivity. Proc Natl Acad Sci USA 69: 1900-1904, July 1972.

1194. Gazdar, A.F. and Ikawa, Y.: Synthetic RNA and DNA polynucleotides; in vivo and in vitro enhancement of oncogenesis by a murine sarcoma virus. Proc Soc Exp Biol Med (In Press).

1195. Gazdar, A.F., Sarma, P., Peebles, P.T. and Chopra, H.C.: Properties of a defective mammalian sarcoma virus. Proc Am Assoc Cancer Res 13: 55, 1972.

1196. Goldberg, R.J., Docherty, J.J. and Rapp, F.: Inhibition of synthesis of Herpes simplex virus deoxyribonucleic acid by a carcinogenic polycyclic aromatic hydrocarbon. Proc Soc Exp Biol Med 140, 1054-1058, 1972.

1197. Inbar, M., Vlodavsky, I. and Sachs, L.: Availability of L-fucose-like sites on the surface membrane of normal and transformed mammalian cells. Biochim Biophys Acta 255: 703-708, 1972.

1198. Jacobsson, H. and Blomgren, H.: Changes of the PHA-responding pool of cells in the thymus after cortisone or x-ray treatment of mice. Evidence for an inverse relation between the production of cortical and medullary thymocytes. Cell Immunol 4: 93-105, 1972.

1199. Klein, G., Dombos, L. and Gothoskar, B.: Sensitivity of Epstein-Barr virus (EBV) producer and non-producer human lymphoblastoid cell lines to superinfection with EB-virus. Int J Cancer 10: 44-57, 1972.

1200. Lee, K.M., Nomura, S., Bassin, R.H. and Fischinger, P.J.: Use of an established cat cell line for investigation and quantitation of feline tumor viruses. J Natl Cancer Inst 49: 50-55, July 1972.

1201. Nomura, S., Fischinger, P.J., Mattern, C.F.T., Peebles, P.T., Bassin, R.H. and Friedman, G.P.: Revertants of mouse cell transformed by sarcoma virus from a sarcoma-positive leukemia-negative cell line. I. Characterization of flat and transformed sublines without a rescuable murine sarcoma virus. Virology (In Press)

1202. Noonan, K.D. and Burger, M.M.: Cell surfaces. McGraw-Hill Science Encyclopedia. (In Press).

1203. Noonan, K.D. and Burger, M.M.: Surface membrane changes in transformed tissue culture cells and possible significance for growth control. 23rd Ann Mtg Tissue Culture Assoc, Los Angeles, 1972 (abstract).

1204. Peters, R.L., Hartley, J.W., Spahn, G.J., Rabstein, L.S., Whitmire, C.E., Turner, H.C. and Huebner, R.J.: Prevalance of the group specific (gs) antigen and infectious virus expressions of the murine C-type RNA viruses during the lifespan of BALB/cCr mice. Int J Cancer (In Press).

1205. Peters, R.L., Rabstein, L.S., Spahn, G.J., Madison, R.M. and Huebner, R.J.: Incidence of spontaneous neoplasms in breeding and retired breeder BALB/cCr mice throughout the natural lifespan. Int J Cancer (In Press).

1206. Peters, R.L., Spahn, G.J., Rabstein, L.S., Turner, G.J. and Huebner, R.J.: Incidence of C-type RNA tumor virus group specific (gs) antigens in spontaneous neoplasms of BALB/cCr mice. Int J Cancer (In Press).

1207. Reusch, V.N., Jr. and Burger, M.M.: Membrane-bound enzymes in protoplast and mesosomal membranes. Fed Proc (In Press).

1208. Schafer, W., Bauer, H., Bolognesi, D.P., Fischinger, P., Frank, H., Gelderblom, H., Lange, J. and Nermut, M.V.: Studies on structural and antigenic properties of C-type viruses. In: Moleuclar Studies in Viral Neoplasia, 25th Annu Symp on Fundamental Cancer Res, Houston, Texas, 1972 (In Press).

1209. Shoham, J. and Sachs, L.: Differences in the binding of fluorescent concanavalin A to the surface membrane of normal and transformed cells. Proc Natl Acad Sci USA (In Press).

1210. Vlodavsky, I., Inbar, M. and Sachs, L.: Temperature sensitive agglutinability of human erythrocytes by lectins. Biochim Biophys Acta 274: 364-369, 1972.

1211. Wollman, J. and Sachs, L.: Mapping of sites on the surface membrane of mammalian cells. II. Relationship of sites for concanavalin A and an ornithine, leucine copolymer. J Membrane Biol (In Press).

1212. Wright, C.S.T., Sato, Y., Nagata, J., McMillan, R., Langridge, M. and Burger, M.M.: X-ray cystallographic studies on a wheat germ glycoprotein whcih agglutinates tumor cells. Fed Proc (In Press).

VIRAL ONCOLOGY
CONTRACTOR DIRECTORY

LISTED IN ALPHABETICAL ORDER

As of September 1, 1972

The purpose of this directory is to facilitate and expedite communications between the VO staff members and VO contractors.

CONTRACTOR : Aichi Cancer Center (69-96)
ADDRESS : Research Institute, Aichi Cancer Center, Tashiro-Cho, Chigusa-ku, Nagoya, Japan
PHONE : AC-052, Phone 762-6111, Ext-731
CNTRCT TITLE: Virus Research Studies in Human Leukemia/Lymphoma Cell Lines
DATES : 5/2/72 - 5/1/73
PRINC INVEST: Dr. Yohei Ito, Laboratory of Viral Oncology
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGEMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Albert Einstein College of Medicine (65-612)
ADDRESS : Yeshiva University, Eastchester Road & Morris Park Avenue, Bronx, New York 10461
PHONE : AC-212, Phone 430-2826
CNTRCT TITLE: Research on Genetics and Immunological Factors in Susceptibility to Murine Leukemia Virus
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Frank Lilly
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Albert Einstein College of Medicine (71-2251)
ADDRESS : Department of Molecular Biology, Yeshiva University, 1300 Morris Park Avenue, Bronx, New York 10461
PHONE : AC-212, Phone 430-2000
CNTRCT TITLE: Studies on The Molecular Basis of Viral Carcinogenesis
DATES : 4/26/72 - 9/30/72
PRINC INVEST: Dr. Joseph August
PROJ OFFICER: Dr. Timothy O'Connor, Bldg. 41, Room A105, x-63647
Dr. Robert Gallo, Bldg. 10, Room 6B18, x-64010
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Atomic Energy Commission (FS-7)
ADDRESS : Oak Ridge National Laboratory, P.O. Box Y, Oak Ridge, Tennessee 37830
PHONE : AC-615, Phone 483-8611, x-37327
CNTRCT TITLE: The Joint AEC-NCI Molecular Anatomy Program
DATES : 9/1/71 - 8/31/72
PRINC INVEST: Dr. Norman G. Anderson
PROJ OFFICER: Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Atomic Energy Commission (72-208)
ADDRESS : Oak Ridge National Laboratories, Oak Ridge, Tennessee 37830
PHONE : AC-615, Phone 483-8611, x-31477
CNTRCT TITLE: Studies in Viral-Chemical Co-Carcinogenesis
DATES : 7/1/71 - 8/31/72
PRINC INVEST: Dr. James Liverman, Biology Division
PROJ OFFICER: Dr. Bernard Talbot, Federal Bldg., Room 504, x-66135
Dr. George Todaro, Federal Bldg., Room 504, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Building, Room 504, x-66135
CNTRCT SPEC : Mr. Maurice Fortin, Bldg. 37, Room 1A07, x-65025

CONTRACTOR : Baylor University College of Medicine (68-678)
ADDRESS : Texas Medical Center, Houston, Texas 77025
PHONE : AC-713, Phone 529-4951, x-403
CNTRCT TITLE: Studies on Viruses as Related To Cancer With Emphasis on Leukemia and Continuation of Testing Program in Primates
DATES : 2/1/71 - 1/3/73
PRINC INVEST: Dr. Joseph L. Melnick
PROJ OFFICER: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Baylor University College of Medicine (72-2058)
ADDRESS : 1200 Moursund Avenue, Texas Medical Center, Houston, Texas 77025
PHONE : AC-713, Phone 529-4951
CNTRCT TITLE: Nonsense Suppressor Mutants for 3T3 Cells
DATES : 1/24/72 - 1/23/73
PRINC INVEST: Dr. C. Thomas Caskey, Department Medicine and Biochemistry
PROJ OFFICER: Dr. Edward M. Scolnick, Federal Bldg., Room 504, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Biolabs (72-2068)
ADDRESS : P.O. Box 32, Prarie View, Illinois 60069
PHONE : AC-312, Phone 362-0890
CNTRCT TITLE: Development and Evaluation of Methods for Preparation of Purified Oncogenic Herpesvirus Especially Epstein-Barr Virus
DATES : 12/20/71 - 12/19/72
PRINC INVEST: Dr. Clyde R. Goodheart
PROJ OFFICER: Dr. Dharam V. Ablashi, Bldg. 37, Room 2C16, x-65276
Dr. Robert J. Goldberg, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Bionetics Research Laboratories, Inc. (69-2160)
ADDRESS : 5510 Nicholson Lane, Kensington, Maryland 20795
PHONE : AC-301, Phone 881-5600
CNTRCT TITLE: Support Services for the Special Virus Cancer Program
DATES : 10/27/71 - 10/26/72
PRINC INVEST: Dr. David Valerio
PROJ OFFICER: Dr. Robert Bassin, Building 41, Room 400, x-66588
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACT : California State Department of Public Health (69-87)
ADDRESS : 2151 Berkeley Way, Berkeley, California 94704
PHONE : AC-415, Phone 843-7900
CNTRCT TITLE: Cancer in Households: A Human-Feline Retrospective Study
DATES : 11/1/71 - 10/31/72
PRINC INVEST: Dr. Robert Schneider
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Padman S. Sarma, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California State Department of Public Health (69-997)
ADDRESS : 2151 Berkeley Way, Berkeley, California 94704
PHONE : AC-415, Phone 843-7900, x-514
CNTRCT TITLE: Studies on the Possible Role of Oncogenic Viruses in the Causation of Cancer in Man and His Domestic Animals
DATES : 6/24/71 - 6/30/72
PRINC INVEST: Dr. Edwin Lennette, Viral and Rickettsial Disease Laboratory
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Padman S. Sarma, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (63-13)
ADDRESS : School of Public Health, Oakland, California 94625
PHONE : AC-415, Phone 832-5217
CNTRCT TITLE: Cell Reagents and Research in Viral Carcinogenesis
DATES : 11/1/71 - 9/30/72
PRINC INVEST: Dr. Stuart H. Madin
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Jack Gruber, Bldg. 37, Room 1D15, x- 61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (70-2048)
ADDRESS : School of Veterinary Medicine, Davis, California 95616
PHONE : AC-916, Phone 752-1341
CNTRCT TITLE: Comparative Leukemia and Sarcoma Virus Studies
DATES : 5/1/72 - 4/30/73
PRINC INVEST: Dr. Leo Bustad, Laboratory of Comparative Oncology
PROF OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Wade Parks, Bldg. 37, Room 1B22, x-65967
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (70-2202)
ADDRESS : P.O. Box 109, La Jolla, California 92037
PHONE : AC-714, Phone 453-2000, x-2538
CNTRCT TITLE: Development and Operation of A Breeding Colony of Domestic Cats
DATES : 6/23/71 - 6/22/72
PRINC INVEST: Dr. Alexis Kniazeff, Division of Animal Resources
PROJ OFFICER: Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
Miss Marie Purdy, Federal Bldg., Room 504, x-66085
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (71-2147)
ADDRESS : 1326 3rd Avenue, San Francisco, California 94122
PHONE : AC-415, Phone 666-9000, x-2824
CNTRCT TITLE: Study on the Role of Virion-Associated DNA Polymerase
DATES : 5/3/72 - 5/2/73
PRINC INVEST: Dr. Michael J. Bishop, Department of Microbiology
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Frank Portugal, Bldg. 37, Room 2C11, x-66461
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (71-2173)
ADDRESS : 118 California Hall, Berkeley, California 94720
PHONE : AC-415, Phone 642-0942
CNTRCT TITLE: Studies on The Structure and Replication of Viruses and Mechanisms of Regulation
DATES : 6/29/71 - 6/30/72
PRINC INVEST: Dr. Howard K. Schachman, Virus Laboratory
PROJ OFFICER: Dr. Bernard Talbot, Federal Bldg., Room 504, x-66135
Dr. Peter Fischinger, Building 41, Room A117, x-66588

SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : California, University of (72-2008)
ADDRESS : 405 Hilgard Avenue, Los Angeles California 90024
PHONE : AC-213, Phone 825-7651
CNTRCT TITLE: Cellular Immunity to Tumor Antigens
DATES : 7/12/71 - 7/11/72
PRINC INVEST: Dr. Paul I. Terasaki, Department of Surgery
PROJ OFFICER: Dr. Ernest Plata, Bldg. 41, Room 300, x-66178
Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : California, University of (72-2080)
ADDRESS : Davis, California 95616
PHONE : AC-916, Phone 752-3179
CNTRCT TITLE: In Vitro Cultivation of Human and Mouse Mammary Tumor Virus
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Robert D. Cardiff
PROJ OFFICER: Dr. Robert Depue, Bldg. 31, Room 11A11, x-66271
SEGMENT : Breast Cancer
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-65121

CONTRACTOR : California, University of (72-3226)
ADDRESS : School of Medicine, The Center for Health Sciences, Los Angeles, California 90024
PHONE : AC-213, Phone 825-5245
CNTRCT TITLE: Search for Viral DNA in Tissues From Cancer Patients
DATES : 6/8/72 - 1/31/73
PRINC INVEST: Dr. Marcel Baluda
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : California, University of (72-3236)
ADDRESS : San Francisco Medical Center, San Francisco, California 94112
PHONE : AC-415, Phone 666-4132
CNTRCT TITLE: Effect of Oncogenic Viral Transformation on The Regulation of Gene Expression in Cultured Mammalian Cells
DATES : 4/26/72 - 4/25/73
PRINC INVEST: Dr. Gordon Tomkins
PROJ OFFICER: Dr. Bernard Talbot, Federal Bldg., Room 504, x-66135
Dr. Stuart Aaronson, Federal Bldg., Room 504, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Center for Disease Control (VCL-42)
ADDRESS : 1600 Clifton Road, N.E., Atlanta, Georgia 30322
PHONE : AC-404, Phone 633-3311
CNTRCT TITLE: Etiologic Studies of Leukemia and Related Disease Occurring in Unusual Epidemiological or Genetic Situations
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Dr. Clark W. Heath, Jr., Epidemiology Program
PROJ OFFICER: Dr. Adi Gazdar, Bldg. 41, Room 200, x-61200
Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Chicago Park District (Lincoln Park Zoo) (65-1017)
ADDRESS : 100 West Webster, Chicago, Illinois 60614
PHONE : AC-312, Phone 549-3000
CNTRCT TITLE: Marmoset Breeding Colony
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. Lester Fisher
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Children's Hospital of D.C. (72-2071)
ADDRESS : 2125 13th Street, N.W., Washington, D.C. 20009
PHONE : AC-202, Phone 835-4000
CNTRCT TITLE: A Study of Cell-Mediated Responses in Pediatric Cancers
DATES : 2/1/72 - 1/31/72
PRINC INVEST: Dr. Sanford Leiken
Dr. John Lilly
PROJ OFFICER: Dr. Berton Zbar, Bldg. 37, Room 2B09, x-66141
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Children's Hospital of Philadelphia (66-477)
ADDRESS : 1740 Bainbridge Street, Philadelphia, Pennsylvania 19146
PHONE : AC-215, Phone 546-2700
CNTRCT TITLE: Immunofluorescence Studies of Human Leukemia, Lymphomas
DATES : 2/4/72 - 1/31/73
PRINC INVEST: Dr. Gertrude Henle, Research Department
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. George Burton, Federal Bldg., Room 508, x-66085
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Colorado, University of (69-2080)
ADDRESS : Medical Center, 4200 East Ninth Avenue, Denver, Colorado 80220
PHONE : AC-303, Phone 394-8471
CNTRCT TITLE: Collection of Pediatric Tumor Specimens
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. William E. Hathaway, Department of Pediatrics
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Columbia University (70-2049)
ADDRESS : Institute for Cancer Research, College of Physicians and Surgeons, 99 Fort Washington Avenue, New York, New York 10032
PHONE : AC-212, Phone 579-8582
CNTRCT TITLE: RNA and RNA Replicases in Tumor Cells Associated With RNA Oncogenic Viruses
DATES : 3/1/72 - 1/31/73
PRINC INVEST: Dr. Sol Spiegelman
PROJ OFFICER: Dr. Timothy O'Connor, Bldg. 41, Room A105, x-63647
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Connecticut, University of (69-52)
ADDRESS : College of Agriculture, Storrs, Connctict 06268
PHONE : AC-203, Phone 429-3311
CNTRCT TITLE: Establishment of A Specific Pathogen Free Flock of White Leghorn Chickens
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. Roy E. Luginbuhl, Department of Animal Diseases
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Cornell Univ., N.Y. State Veterinary College (70-2224)
ADDRESS : Ithaca, New York 14850
PHONE : AC-607, Phone 256-2034
CNTRCT TITLE: Feline Tumor Viral Diagnostic Laboratory
DATES : 6/25/71 - 6/24/72
PRINC INVEST: Dr. James Gillespie, Department of Microbiology
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. David M. Howell, Bldg, 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Cornell Univ., N.Y. State Veterinary College (71-2508)
ADDRESS : Ithaca, New York 14850
PHONE : AC-607, Phone 256-5014
CNTRCT TITLE: Leukemia Studies in The Cat
DATES : 6/23/71 - 6/22/72
PRINC INVEST: Dr. Charles Rickard, Department of Pathology
PROJ OFFICER: Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Dow Chemical Company (65-1045)
ADDRESS : P.O. Box 10, Zionsville, Indiana 46077
PHONE : AC-317, Phone 638-2521
CNTRCT TITLE: Research and Development of Biohazards Containment Facilities
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Mr. Cyril Henke, Environmental Bio-Engineering
PROJ OFFICER: Mr. W. Emmett Barkley, Bldg. 41, Room A118, x-66981
Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Duke University (71-2132)
ADDRESS : Durham, North Carolina 27706
PHONE : AC-919, Phone 684-6468
CNTRCT TITLE: Study and Production of Avian Leukosis Viruses
DATES : 4/19/72 - 4/18/73
PRINC INVEST: Dr. Joseph W. Beard, Department of Surgery
PROJ OFFICER: Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
Dr. John Pearson, Bldg. 37, Room 1D16, x-61478
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Electro-Nucleonics, Inc. (71-2253)
ADDRESS : 4921 Auburn Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 652-7164
CNTRCT TITLE: Development of Propagation Procedures, Purification and Characterization of Viruses
DATES : 5/28/72 - 5/27/73
PRINC INVEST: Dr. John Lemp
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Electro-Nucleonics, Inc. (72-3249)
ADDRESS : 4921 Auburn Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 652-7164
CNTRCT TITLE: Production of Oncogenic or Potentially Oncogenic Viruses
DATES : 3/27/72 - 9/30/72
PRINC INVEST: Dr. John Lemp
PROJ OFFICER: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Emory University (71-2256)
ADDRESS : Yerkes Regional Primate Research Center, Atlanta, Georgia 30322
PHONE : AC-404, Phone 377-2411, x-7974
CNTRCT TITLE: Maintenance of Colony of Irradiated Rhesus Monkeys
DATES : 5/1/72 - 4/30/73
PRINC INVEST: Dr. Harold M. McClure
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Flow Laboratories (65-1012)
ADDRESS : 1710 Chapman Avenue, Rockville, Maryland 20852
PHONE : AC-301, Phone 881-2900
CNTRCT TITLE: Maintenance of A Repository for Storage and Distribution of Reagents and Tissue Specimens
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Mr. Jack W. Walker
PROJ OFFICER: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
Dr. Robert Goldberg, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room A103, x-65025

CONTRACTOR : Flow Laboratories, Inc. (71-2097)
ADDRESS : 1710 Chapman Avenue, Rockville, Maryland 20852
PHONE : AC-301, Phone 881-2900, x-272
CNTRCT TITLE: Studies of Herpes Viruses and C-Type Viruses in Relation to Oncogenic Potential
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Raymond V. Gilden
PROJ OFFICER: Dr. Robert J. Huebner, Bldg. 37, Room 2D24, x-63301
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Berge Hampar, Bldg. 37, Room 1B22, x-65967
Dr. Wade Parks, Bldg.Room 1B22, x-65967
Dr. Kenneth Rand, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Flow Laboratories, Inc. (71-2341)
: 1710 Chapman Avenue, Rockville, Maryland 20852
PHONE : AC-301, Phone 881-2900
CNTRCT TITLE: The Provision of An Animal Holding Facility
DATES : 6/18/71 - 6/17/72
PRINC INVEST: Dr. W. Knapp
PROJ OFFICER: Dr. John Pearson, Bldg. 37, Room 1D16, x-61478
Dr. Adi Gazdar, Bldg. 41, Room 200, x-61200
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : George Washington University (72-3251)
ADDRESS : 2300 K Street, N.W., Washington, D.C. 20037
PHONE : AC-202, Phone 331-3562
CNTRCT TITLE: Clinical Tests for Mutant Responses to Separated Soluble Membrane Antigens Which Appear To Be Tumor-Specific
DATES : 4/13/72 - 4/12/73
PRINC INVEST: Dr. T. Crandall Alford
PROJ OFFICER: Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Georgetown University (65-53)
ADDRESS : 3800 Reservoir Road, Washington, D.C. 20007
PHONE : AC-202, Phone 625-7368
CNTRCT TITLE: Human Breast Cancer Virus Studies
DATES : 12/1/71 - 11/30/72
PRINC INVEST: Dr. William F. Feller
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
Mr. John Kvedar, Bldg. 41, VTPL, x-65341
Dr. Louis Sibal, Bldg. 37, Room 1A15, x-62796
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Georgetown University (72-3248)
ADDRESS : 3800 Reservoir Road, N.W., Washington, D.C. 20007
PHONE : AC-202, Phone 652-7459
CNTRCT TITLE: Supply of Blood Tissue Specimens From Patients With Malignancies
DATES : 6/28/72 - 6/27/73
PRINC INVEST: Dr. Gerald Sandler
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Robert J. Goldberg, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Germfree Life Research Center (72-3261)
ADDRESS : 3301 College Avenue, Fort Lauderdale, Florida 33312
PHONE : AC-305, Phone 587-6660, x-235
CNTRCT TITLE: Germfree Life and Oncogenesis
DATES : 5/1/72 - 4/30/73
PRINC INVEST: Dr. Joel Warren
PROJ OFFICER: Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
Dr. Robert J. Goldberg, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Harvard University (72-3246)
ADDRESS : New England Regional Primate Center, 1 Pine Hill Drive, Southborough, Massachusetts 01772
PHONE : AC-617, Phone 481-0400
CNTRCT TITLE: Isolation and Characterization of DNA Viruses Associated With Primate Tumors
DATES : 6/26/72 -
PRINC INVEST: Dr. Luis Melendez
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Hazleton Laboratories, Inc. (69-2079)
ADDRESS : P.O. Box 30, Falls Church, Virginia 22046
PHONE : AC-703, Phone 893-5400
CNTRCT TITLE: Etiology of Cancer in Dogs
DATES : 9/1/71 - 6/30/72
PRINC INVEST: Dr. Robert C. Good
PROJ OFFICER: Dr. Stuart Aaronson, Federal Bldg., Room 504, x-66135
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Health Research, Inc. (72-2014)
ADDRESS : Roswell Park Institute, 666 Elm Street, Buffalo, New York 14203
PHONE : AC-716, Phone 845-2300
CNTRCT TITLE: Stimulation of Immunity Against Tumor By Enzymatically Treated Autochthonous Tumor Cells
DATES : 9/15/71 - 9/14/72
PRINC INVEST: Dr. James Holland
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Health Research, Inc. (72-3247)
ADDRESS : Roswell Park Institute, 666 Elm Street, Buffalo, New York 14203
PHONE : AC-716, Phone 845-3010
CNTRCT TITLE: Supply of Blood and Tissue Specimens From Patients With Malignancies
DATES :
PRINC INVEST: Dr. Joseph Sokal
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Hospital For Sick Children (72-3266)
ADDRESS : 555 University Avenue, Toronto 2, Ontario, Canada
PHONE : AC-416, Phone 366-7242
CNTRCT TITLE: Collection of Specimens from Human Pediatric Leukemia Patients and Non-Leukemia Controls
DATES : 6/1/71 - 5/31/72
PRINC INVEST: Dr. Peter D. McClure, Division of Hematology
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Hospital St. Louis (72-3263)
ADDRESS : Institut de Recherches Sur Les Leucemies, Paris, France
PHONE :
CNTRCT TITLE: Molecular Virology Studies on Human Leukemia
DATES :
PRINC INVEST: Dr. M. Boiron
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66085
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Howard University Medical School (70-2178)
ADDRESS : 6th and Bryant Streets, N.W., Washington, D.C. 20001
PHONE : AC-202, Phone 636-6357
CNTRCT TITLE: Immunological Studies of Human Mammary Tumors and Other Neoplasms
DATES : 5/1/72 - 4/30/73
PRINC INVEST: Dr. Michael Viola Department of Medicine
PROJ OFFICER: Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
Dr. Dan Rubin, Bldg. 37, Room 1B19, x-62760
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg. Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Huntingdon Research Center (69-54)
ADDRESS : P.O. Box 6857, Baltimore, Maryland 21204
PHONE : AC-301, Phone 825-3484
CNTRCT TITLE: Fluorescent Antibody Studies of Indigenous Mouse Viruses
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. Roger Wilsnack
PROJ OFFICER: Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
Dr. Wallace Rowe, Bldg. 7, Room 304, x-62613
Dr. Robert J. Goldberg, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Illinois, University of (72-2031)
ADDRESS : P.O. Box 6998, Chicago, Illinois 60680
PHONE : AC-312, Phone 663-7067
CNTRCT TITLE: Molecular Mechanisms of Carcinogenesis By Oncogenic Viruses
DATES : 12/9/71 - 12/8/72
PRINC INVEST: Dr. Giampiero Dimayorca, Department of Microbiology
PROJ OFFICER: Dr. Bernard Talbot, Federal Bldg., Room 504, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Institute For Medical Research (68-1000)
ADDRESS : Sheridan and Copewood Streets, Camden, New Jersey 08103
PHONE : AC-609, Phone 966-7377
CNTRCT TITLE: Studies of Human Milk and Mammary Tumors
DATES : 4/29/72 - 4/30/73
PRINC INVEST: Dr. Dan Moore
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : International Agency for Research on Cancer (70-2076)
ADDRESS : 16 Avenue Marechal Foch, 69, Lyon, France
PHONE : AC-78, Phone 52-32-40
CNTRCT TITLE: Sero-Epidemiological Studies on Naso-Pharyngeal Carcinoma and Burkitt's Lymphoma
DATES : 1/1/72 - 12/31/72
PRINC INVEST: Dr. Guy Blaudin de The
PROJ OFFICER: Dr. Robert DePue, Bldg. 31, Room 11A11, x-66271
Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Dan Rubin, Bldg. 37, Room 1B19, x-62760
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Jackson Memorial Laboratory (67-744)
ADDRESS : Bar Harbor, Maine 04609
PHONE : AC-207, Phone 288-3373
CNTRCT TITLE: Murine Leukemia-Sarcoma Complex: Natural Occurence of Leukemia Virus and The Sarcoma Genome in Mice
DATES : 5/1/72 - 4/30/73
PRINC INVEST: Dr. Hans Meier
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Gary Kelloff, Bldg. 37, Room 2C07, x-61320
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Jewish Hospital and Medical Center of Brooklyn (72-2034)
ADDRESS : 555 Prospect Place, Brooklyn, New York 11238
PHONE : AC-212, Phone Ulster 7-8700
CNTRCT TITLE: Viral Transformation and Chromosome Abnormalities in Human Tumors
DATES : 10/16/71 - 8/31/72
PRINC INVEST: Dr. Harvey Dosik
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Johns Hopkins University (69-2008)
ADDRESS : School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205
PHONE : AC-301, Phone 955-3459
CNTRCT TITLE: Maintenance of A Foundation Colony of Leukosis-Free Chickens
DATES : 3/24/72 - 6/30/72
PRINC INVEST: Dr. Frederick B. Bang, Department of Pathology
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
Mr. John Kvedar, Bldg. 41, VTPL, x-65341
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Johns Hopkins University (71-2109)
ADDRESS : Charles and 34th Streets, Baltimore, Maryland 21218
PHONE : AC-301, Phone 955-3300
CNTRCT TITLE: Anti-tumor Reactivity in Patients With Leukemia/Lymphoma
DATES : 5/1/72 - 5/30/73
PRINC INVEST: Dr. George W. Santos, Department of Medicine
PROJ OFFICER: Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
Dr. Dan Rubin, Bldg. 37, Room 1B19, x-62760
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Johns Hopkins University (71-2121)
ADDRESS : Charles and 34th Streets, Baltimore, Maryland 21218
PHONE : AC-301, Phone 955-3273
CNTRCT TITLE: Studies on Herpes Virus Antigens and Virions in Neoplastic Cells From Cervical Carcinoma
DATES : 5/5/72 - 5/4/73
PRINC INVEST: Dr. Laure Aurelian, Division of Laboratory Animal Medicine
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Karolinska Institutet (69-2005)
ADDRESS : S-104 01, Stockholm 60, Sweden
PHONE : 235-480
CNTRCT TITLE: Studies of The Significance of Herpes-Type Virus in The Etiology of Some Human Cancers
DATES : 4/9/72 - 4/8/73
PRINC INVEST: Dr. George Klein, Department of Tumor Biology
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Life Sciences, Inc. (68-711)
ADDRESS : 2950 72nd Street, North, St. Petersburg, Florida 33710
PHONE : AC-813, Phone 345-9371
CNTRCT TITLE: Production and Maintenance of Germfree and Selected Reagent Grade SPF Animals
DATES : 8/1/71 - 7/31/72
PRINC INVEST: Dr. Wendall Farrow
PROJ OFFICER: Mr. John Kvedar, Bldg. 41, VTPL, x-65341
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Life Sciences, Inc. (69-63)
ADDRESS : 2950 72nd Street, North, St. Petersburg, Florida 33710
PHONE : AC-813, Phone, 347-6191
CNTRCT TITLE: Studies on Marek's Disease as A Model For Herpesvirus-Associated Oncogenesis
DATES : 8/1/71 - 7/31/72
PRINC INVEST: Dr. Jack W. Frankel
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Litton Bionetics, Inc. (71-2025)
ADDRESS : 5510 Nicholson Lane, Kensington, Maryland 20795
PHONE : AC-301, Phone 881-5600
CNTRCT TITLE: Investigation of The Carcinogenic Activity of Selected Virus Preparation in The Newborn Monkey
DATES : 9/1/71 - 8/31/72
PRINC INVEST: Dr. Harvey Rabin
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Louisville, University of (66-902)
ADDRESS : School of Medicine, Preston and Walnut Streets, Louisville, Kentucky 40201
PHONE : AC-502, Phone 582-2211, x-335
CNTRCT TITLE: Studies on Foamy Virus Reagents and Antisera
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Dr. Paul B. Johnston, Department of Microbiology
PROJ OFFICER: Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Makerere University Medical School (67-47)
ADDRESS : P.O. Box 2072, Kampala, Uganda, East Africa
PHONE :
CNTRCT TITLE: Epidemiological Investigation of Burkitt's Lymphoma in Uganda
DATES : 9/26/71 - 9/25/72
PRINC INVEST: Dr. George Kafuko, East Africa Virus Research Institute
PROJ OFFICER: Dr. Robert Depue, Bldg. 31, Room 11A11, x-66271
Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Mason Research Institute (70-2204)
ADDRESS : Harvard Street, Worcester, Massachusetts 01608
PHONE : AC-617, Phone 752-4601
CNTRCT TITLE: Study on The Role of Hormonal Factors on Induction of Breast Tumors
DATES : 6/7/72 - 6/6/73
PRINC INVEST: Dr. Marcus M. Mason
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
Dr. Jane Taylor, Federal Bldg., Room 4C04, x-66718
Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Massachusetts General Hospital (71-2174)
ADDRESS : John Collins Warren Laboratory, Boston, Massachusetts 02114
PHONE : AC-617, Phone 726-3671
CNTRCT TITLE: Transfer RNA Studies
DATES : 6/29/71 - 6/28/72
PRINC INVEST: Dr. Paul Zamecnik
PROJ OFFICER: Dr. Timothy O'Connor, Bldg. 41, Room A105, x-63647
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Massachusetts General Hospital (72-2012)
ADDRESS : Harvard Medical School, Fruit Street, Boston, Massachusetts 02114
PHONE : AC-617, Phone 726-3812
CNTRCT TITLE: Activation of Oncogenic Viruses and Induction of Cancer By Immunologic and Non-Immunologic Methods
DATES : 9/15/71 - 9/14/72
PRINC INVEST: Dr. Paul H. Black, Infectious Disease Unit
PROJ OFFICER: Dr. Adi Gazdar, Bldg. 41, Room 200, x-61200
Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Massachusetts Institute of Technology (71-2149)
ADDRESS : Cambridge, Massachusetts 02139
PHONE : AC-617, Phone 846-6900, x-4725
CNTRCT TITLE: Studies on RNA Dependent DNA Polymerase
DATES : 5/1/71 - 4/30/72
PRINC INVEST: Dr. David Baltimore, Division of Sponsored Research
PROJ OFFICER:
Dr. Edward M. Scolnick, Federal Bldg., Room 504, x-66135
Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg.,Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Medical College of Wisconsin (68-1010)
ADDRESS : 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 63226
PHONE : AC-414, Phone 344-1000
CNTRCT TITLE: Protein and Steroid Hormone Effects on Virus Production in C-Particle-Containing Cancer Cells In Vitro
DATES : 12/1/71 - 11/30/72
PRINC INVEST: Dr. Roland Patillo, Colony Hospital (AC-414, Phone 258-4774)
PROJ OFFICER: Dr. Robert Depue, Bldg. 31, Room 11A11, x-66271
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Meloy Laboratories, Inc. (72-2006)
ADDRESS : 6631 Iron Place, Springfield, Virginia 22150
PHONE : AC-703, Phone 354-2600
CNTRCT TITLE: Spontaneous and Virus-Induced Neoplastic Transformation
DATES : 8/20/71 - 8/19/72
PRINC INVEST: Dr. John Verna
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 504, x-66135
Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Meloy Laboratories, Inc. (72-2020)
ADDRESS : 6631 Iron Place, Springfield, Virginia 22150
PHONE : AC-703, Phone 354-2600, x-282
CNTRCT TITLE: Cell Biology Facility
DATES : 8/20/71 - 8/19/72
PRINC INVEST: Dr. Kenneth Blackman
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. J. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Meloy Laboratories, Inc. (72-2306)
ADDRESS : 6631 Iron Place, Springfield, Virginia 22151
PHONE : AC-703, Phone 354-2600
CNTRCT TITLE: Collaborative Project On The Oncogenic Potential of Herpesviruses in Primates
DATES : 3/30/72 - 3/29/73
PRINC INVEST: Dr. John Sever
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Meloy Laboratories, Inc. (72-3202)
ADDRESS : 6631 Iron Place, Springfield, Virginia 22151
PHONE : AC-703, Phone 354-2600
CNTRCT TITLE: Bioassays of Mouse Mammary Tumor Virus
DATES : 8/20/71 - 8/19/72
PRINC INVEST: Dr. John Verna
PROJ OFFICER: Dr. Louis Sibal, Bldg. 37, Room 1A15, x-62796
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Memorial Hospital For Cancer and Allied Diseases (71-2116)
ADDRESS : 494 East 68th Street, New York, New York 10021
PHONE : AC-212, Phone 879-3000
CNTRCT TITLE: Acquisition of Human Materials to Be Used In The Search for Transmissable Agents in Human Tumors
DATES : 3/1/72 - 3/17/73
PRINC INVEST: Dr. Yashar Hirshaut, Division of Cell Biology
PROJ OFFICER: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Memorial Hospital For Cancer and Allied Diseases (71-2194)
ADDRESS : 494 East 68th Street, New York, New York 10021
PHONE : AC-212, Phone 879-3000
CNTRCT TITLE: Collection of Breast Cancer Specimens
DATES : 6/25/71 - 6/24/72
PRINC INVEST: Dr. Herbert F. Oettgen
PROJ OFFICER:
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Merck and Company (71-2059)
ADDRESS : West Point, Pennsylvania 19486
PHONE : AC-215, Phone 699-5311, x-5532
CNTRCT TITLE: Oncogenic Virus Research and Vaccine Development
DATES : 12/1/71 - 11/30/72
PRINC INVEST: Dr. Maurice R. Hilleman, Virus and Cell Biology Research
PROJ OFFICER: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Miami, University of (67-1187)
ADDRESS : School of Medicine, P.O. Box 7278, Miami, Florida 33155
PHONE : AC-305, Phone 284-2590
CNTRCT TITLE: Immunization Studies On Avian Leukosis and Related Problems
DATES : 6/23/71 - 6/22/72
PRINC INVEST: Dr. Michael Siegel
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. George Burton, Federal Bldg., Room 508, x-66085
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Miami, University of (70-2211)
ADDRESS : School of Medicine, P.O. Box 7278, Miami, Florida 33155
PHONE : AC-305, Phone 284-2590
CNTRCT TITLE: Studies on The Rat Mammary Tumor-Derived-Virus (RMTDV or BV)
DATES : 11/1/71 - 6/30/72
PRINC INVEST: Dr. Victor V. Bergs, Department of Microbiology
PROJ OFFICER: Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Michigan Cancer Foundation (71-2421)
ADDRESS : 4811 John R. Street, Detroit, Michigan 48201
PHONE : AC-313, Phone 833-0710
CNTRCT TITLE: Studies of High Risk Breast Cancer Families
DATES : 6/20/71 - 6/19/72
PRINC INVEST: Dr. Michael J. Brennan
PROJ OFFICER:
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Michigan, University of (65-639)
ADDRESS : Medical School, Ann Arbor, Michigan 48105
PHONE : AC-313, Phone 764-8100
CNTRCT TITLE: Collection of Leukemia/Lymphoma Specimens; FA Studies; Viral Genome Rescue Studies
DATES : 9/1/71 - 8/31/72
PRINC INVEST: Dr. Chris J.D. Zarafonetis, Department of Microbiology
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Robert Goldberg, Bldg. 37, Room 1D21, x-61718
Dr. Deward Waggoner, Federal Bldg., Room 508, x-64148
SEGMENT : Program Resources and Logistics
SEG CHARIMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Microbiological Associates, Inc. (66-914)
ADDRESS : 4733 Bethesda Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 654-3400, x-300
CNTRCT TITLE: Operation of A Balb/C Mouse Colony
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Mr. Wilbur Athey
PROJ OFFICER: Dr. Samuel Poiley, Bldg. 37, Room 5E10, x-61323
Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
Mr. Clarence Reeder, Bldg. 37, Room 5E12A, x-61323
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Microbiological Associates, Inc. (67-697)
ADDRESS : 4733 Bethesda Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 654-3400
CNTRCT TITLE: Detection, Characterization and Assay of Animal Tumor Viruses
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Robert M. Nims
PROJ OFFICER: Dr. Gary Kelloff, Bldg. 37, Room 2C07, x-61320
Dr. Robert J. Huebner, Bldg. 37, Room 2D24, x-63301
Mr. John Kvedar, Bldg. 41, VTPL, x-65341
SEGMENT : Solid Tumor Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Microbiological Associates, Inc. (67-700)
ADDRESS : 4733 Bethesda Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 654-3400
CNTRCT TITLE: Mouse Virus Typing and Diagnostic Reagents
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. John Parker
PROJ OFFICER: Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
Dr. Wallace Rowe, Bldg. 7, Room 304, x-62613
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHARIMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Microbiological Associates, Inc. (70-2068)
ADDRESS : 4733 Bethesda Avenue, Bethesda, Maryland 20014
PHONE : AC-301, Phone 654-3400
CNTRCT TITLE: The Roles of Viruses and Chemicals in The Etiology of Cancer
DATES : 10/22/71 - 10/22/72
PRINC INVEST: Dr. Riley Housewright
PROJ OFFICER: Dr. Robert J. Huebner, Bldg. 37, Room 2D24, x-63301
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Padman S. Sarma, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Minnesota, University of (69-2061)
ADDRESS : College of Medical Sciences, Minneapolis, Minnesota 55455
PHONE : AC-612, Phone 373-7733
CNTRCT TITLE: Tumor-Specific Transplantation Antigens in Solid Tumors
DATES : 6/15/72 - 6/14/73
PRINC INVEST: Dr. Charles F. McKhann, Department of Surgery
PROJ OFFICER: Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Minnesota, University of (71-2261)
ADDRESS : College of Medical Sciences, 315 Morrill Hall, Minneapolis, Minnesota 55455
PHONE : AC-612, Phone 373-7733
CNTRCT TITLE: Immunological Deficiency Diseases and Cancer
DATES : 5/13/71 - 5/12/72
PRINC INVEST: Dr. John Kersey
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Minnesota, University of (72-2066)
ADDRESS : School of Public Health, Minneapolis, Minnesota 55455
PHONE : AC-612, Phone 373-3167
CNTRCT TITLE: Development of Short Courses On The Principles of Biohazard and Injury Control For The Biomedical Laboratory
DATES : 12/10/71 - 12/9/72
PRINC INVEST: Prof. George Michaelson, Division of Environmental Health
PROJ OFFICER: Mr. W. Emmett Barkley, Bldg. 41, Room A118, x-66981
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Montreal Children's Hospital (65-1020)
ADDRESS : 2300 Tupper Street, Montreal 25, Quebec, Canada
PHONE : AC-514, Phone 937-8511
CNTRCT TITLE: Procurement of Blood Plasma/Serum Specimens From Human Leukemic, Malignant Tumor and Non-Leukemic Controls, Including Family Members, Among Patients Of The Montreal Children's Hospital and Performance of Certain Laboratory Procedures Upon Such Specimens
DATES : 6/1/72 - 5/31/73
PRINC INVEST: Dr. Ronald L. Denton, Department of Hematology
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Naples, University of (71-2056)
ADDRESS : Piazza Miraglia, (1-Cattedra), Naples, Italy
PHONE : 218-524 (PBX)
CNTRCT TITLE: Studies in The Role of HSV Types 1 and 2 in Human Malignancies
DATES : 4/9/72 - 4/8/73
PRINC INVEST: Dr. Guillio Tarro, Institute of Pathology
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Naval Biomedical Research Laboratories (FS-8)
ADDRESS : U.S. Naval Supply Center, Oakland, California 94625
PHONE : AC-415, Phone 832-5217
CNTRCT TITLE: Facility For Cell Culture Research
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Capt. Thomas G. Akens, MSC, USN
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1A03, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Naval Biomedical Research Laboratories (FS-57)
ADDRESS : U.S. Naval Supply Center, Oakland, California 94625
PHONE : AC-415, Phone 832-5217
CNTRCT TITLE: Studies of Environmental and Physiological Factors Influencing Virus-Host With Interaction
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Dr. R.L. Dimmick
Dr. M.A. Chatigny
PROJ OFFICER: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
Dr. Arnold Fowler, Bldg. 41, Room A103, x-66758
Mr. W. Emmett Barkley, Bldg. 41, Room A118, x-66981
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room A103, x-65025

CONTRACTOR : New York Medical College (72-3289)
ADDRESS : Flower and 5th Avenue Hospital, 5th Avenue at 106th Street, New York, New York 10029
PHONE : AC-212, Phone 876-5500
CNTRCT TITLE: Immunological Responses of Breast Cancer Patients Against Autologous Breast Cancer Tissues
DATES :
PRINC INVEST: Dr. Maurice Black
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Netherlands Cancer Institute (72-3260)
ADDRESS : Sarphatistraat 108, Amsterdam C, The Netherlands
PHONE : AC-020, Phone 943-434
CNTRCT TITLE: Immunogenetic Studies of Breast Cancer and Leukemia
DATES : 6/27/72 - 1/1/73
PRINC INVEST: Dr. Lourens M. Boot
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : North Carolina, University of (72-3228)
ADDRESS : 503 Swing Building, School of Medicine, Chapel Hill, North Carolina 27514
PHONE : AC-919, Phone 966-1184
CNTRCT TITLE: Molecular Biological Studies of Epstein-Barr Virus Infection and Related Herpesviruses in Human Diseases
DATES :
PRINC INVEST: Dr. Joseph Pagano
PROJ OFFICER: Dr. Timothy O'Connor, Bldg. 41, Room A105, x-63647
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : North Dakota, University of (66-8)
ADDRESS : School of Medicine, Grand Forks, North Dakota 58202
PHONE : AC-701, Phone 777-2411
CNTRCT TITLE: Quantitative Studies on The Transmission of Feline Oncogenic RNA Viruses and Selected Herpesviruses By Certain Bloodsucking Anthropods
DATES : 1/1/72 - 12/31/72
PRINC INVEST: Dr. Robert Fischer, Department of Microbiology
PROJ OFFICER: Dr. George Burton, Federal Bldg., Room 508, x-66085
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Ohio State University (65-1001)
ADDRESS : Veterinary Pathology Building, 1925 Coffey Road, Columbus, Ohio 43210
PHONE : AC-614, Phone 422-5661
CNTRCT TITLE: Biohazards Control and Containment in Oncogenic Virus Research
DATES : 7/1/71 - 6/30/72
PRINC INVEST: Dr. David Yohn
PROJ OFFICER: Dr. Alfred Hellman, Bldg.41, Room A103, x-66758
Dr. Arnold K. Fowler, Bldg. 41, Room A103. x-66758
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Ohio State University (69-2233)
ADDRESS : Veterinary Pathology Building, 1925 Coffey Road, Columbus, Ohio 43210
PHONE : AC-614, Phone 293-7621
CNTRCT TITLE: Application of Radioiodine Labelled Antibody Technique To Studies of Virus-Induced Tumors and Human Neoplasms of Suspected Viral Etiology
DATES : 6/27/71 - 6/26/72
PRINC INVEST: Dr. David Yohn
PROJ OFFICER: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Oregon State University (71-2175)
ADDRESS : Corvallis, Oregon 97331
PHONE : AC-503, Phone 754-1945
CNTRCT TITLE: Studies on The Oncogenic Potential of Defective Human Viruses
DATES : 6/28/71 - 6/27/72
PRINC INVEST: Dr. George Beaudreau, Department of Agricultural Chemistry
PROJ OFFICER: Dr. Albert Dalton, Bldg. 37, Room 1C17, x-64311
Dr. Ursula Heine, Bldg. 37, Room 1C17, x-64311
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Padua University Hospital (68-1389)
ADDRESS : Instituto di Chirurgia Plastica, Monoblocco Ospedaliero, 35100, Padua, Italy
PHONE :
CNTRCT TITLE: Procurement of Fibroblast Cultures From Donors With A High Degree of Homozygosity and Procurement From Human Tumors
DATES : 6/7/72 - 6/6/73
PRINC INVEST: Prof. Giovanni Dogo
PROJ OFFICER: Dr. Robert Depue, Bldg. 31, Room 11A11, x-66271
Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A05, x-65025

CONTRACTOR : Pennsylvania State University (70-2024)
ADDRESS : Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033
PHONE : AC-717, Phone 534-8254
CNTRCT TITLE: Studies on The Oncogenic Potential of Defective Human Viruses
DATES : 10/27/71 - 9/30/72
PRINC INVEST: Dr. Fred Rapp, Department of Microbiology
PROJ OFFICER: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Pennsylvania, University of (65-1013)
ADDRESS : School of Veterinary Medicine, New Bolton Center, Kennett Square, R.D. #1, Pennsylvania 19348
PHONE : AC-215, Phone 444-5800
CNTRCT TITLE: Experimental and Natural Transmission of Bovine Leukemia
DATES : 1/1/72 - 7/15/72
PRINC INVEST: Dr. Robert Marshak, Department of Clinical Studies
PROJ OFFICER: Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Pfizer, Inc. (67-1176)
ADDRESS : 199 Maywood Avenue, Maywood, New Jersey 07607
PHONE : AC-201, Phone 845-5665
CNTRCT TITLE: Viral Studies of Human And Animal Breast Cancer
DATES : 6/28/71 - 6/27/72
PRINC INVEST: Dr. Sami A. Mayyasi
PROJ OFFICER: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
Dr. Louis Sibal, Bldg. 37, Room 1A15, x-62796
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Pfizer, Inc. (70-2080)
ADDRESS : 199 Maywood Avenue, Maywood, New Jersey 07607
PHONE : AC-201, Phone 845-5665
CNTRCT TITLE: Development of Virus-Cancer Test System; Virus Production; Production of Human Virus-Cancer Cell Lines; Immunology
DATES : 1/1/72 - 12/31/72
PRINC INVEST: Dr. Sami A. Mayyasi
PROJ OFFICER: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Princeton University (71-2372)
ADDRESS : Princeton, New Jersey 08540
PHONE : AC-609, Phone 452-3864
CNTRCT TITLE: Studies on Surface Alterations in RNA Tumor Virus Cells
DATES : 6/28/71 - 6/27/72
PRINC INVEST: Dr. Max M. Burger, Department of Biochemical Sciences
PROJ OFFICER: Dr. Gary Kelloff, Bldg. 37, Room 2C07, x-61320
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Public Health Research Institute (71-2129)
ADDRESS : 455 1st Avenue, New York, New York 10016
PHONE : AC-212, Phone 340-4600
CNTRCT TITLE: Evaluation of Methods For Isolation of Viruses From Human Neoplasia
DATES : 4/27/72 - 4/26/73
PRINC INVEST: Dr. Hidesaburo Hanafusa, Department of Viral Oncology
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Public Health Research Institute (72-2028)
ADDRESS : 455 1st Avenue, New York, New York 10016
PHONE : AC-212, Phone 340-4415
CNTRCT TITLE: The Relationship Between the Cell Surface Alterations Induced By RNA and DNA Oncogenic Viruses
DATES : 12/3/71 - 12/2/72
PRINC INVEST: Dr. Thomas L. Benjamin, Department of Viral Oncology
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66136
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Research Foundation of State Univ. of New York (71-2137)
ADDRESS : P.O. Box 7126, Albany, New York 12224
PHONE : AC-716, Phone 845-5876
CNTRCT TITLE: Application of Immunotherapy to Proven Curitive for Epidermal Tumors to Other Types of Malignant Diseases
DATES : 5/25/71 - 5/24/72
PRINC INVEST: Dr. Edmund Klein, Department of Dermatology
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Robert B. Brigham Hospital (71-2172)
ADDRESS : Harvard Medical Center, 125 Parker Hill Avenue, Boston, Massachusetts 02120
PHONE : AC-617, Phone 734-5700, x-243
CNTRCT TITLE: Studies on Tumor Specific Transplantation Antigen in Solid Tumors
DATES : 6/28/71 - 6/27/72
PRINC INVEST: Dr. John David, Department of Medicine
PROJ OFFICER: Dr. Charles Boone, Bldg. 37, Room 1C08, x-65141
Dr. Gary Pearson, Bldg 37, Room 1B05, x-62600
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Rush-Presbyterian-St. Luke's Hospital (71-2032)
ADDRESS : 1753 West Congress Parkway, Chicago, Illinois 60612
PHONE : AC-312, Phone 942-5442
CNTRCT TITLE: Studies of Tumor Viruses in Nonhuman Primates
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. Friedrich Deinhardt, Department of Microbiology
PROJ OFFICER: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Rutgers University (71-2077)
ADDRESS : New Brunswick, New Jersey 08903
PHONE : AC-201, Phone 932-2904
CNTRCT TITLE: Test For Genetic Acquisition of Oncogenic Potential and Cell Transforming Capacity by RNA Animal Viruses
DATES : 2/15/72 - 2/14/73
PRINC INVEST: Dr. Robert W. Simpson, Institute of Microbiology
PROJ OFFICER: Dr. Michael Chirigos, Bldg. 37, Room 1D19, x-61478
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Salk Institute (67-1147)
ADDRESS : P.O. Box 1809, San Diego, California 92112
PHONE : AC-714, Phone 453-4100
CNTRCT TITLE: Characterization of Temperature-Sensitive Mutants of Polyoma Virus and Interaction Between Polyoma Virus and C-Type RNA Viruses
DATES : 6/5/72 - 6/4/73
PRINC INVEST: Dr. Walter Eckhart
PROJ OFFICER: Dr. Stuart Aaronson, Bldg. 37, Room 2C07, x-66135
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Salk Institute (72-3207)
ADDRESS : P.O. Box 1809, San Diego, California 92112
PHONE : AC-714, Phone 453-4100, x-308
CNTRCT TITLE: Growth Regulation of Normal and Transformed Cells and Immunological Approaches to Tumor Rejection and Prevention
DATES : 3/6/72 - 1/3/73
PRINC INVEST: Dr. Edwin S. Lennox
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Scripps Clinic and Research Foundation (72-3264)
ADDRESS : 476 Prospect Street, La Jolla, California 92037
PHONE : AC-714, Phone 459-2390, x-301
CNTRCT TITLE: Immunologic Study of RNA Tumor (Type C) Viruses
DATES : 6/29/72 - 6/28/73
PRINC INVEST: Dr. Frank Dixon
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Wade Parks, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Southern California, University of (68-1030)
ADDRESS : Cancer Research Building, 1200 North State Street, Los Angeles, California 90033
PHONE : AC-213, Phone 225-1511, x-384
CNTRCT TITLE: A Comprehensive Field and Laboratory Research Program On The Etiology and Epidemiology of Human Cancer
DATES : 9/1/71 - 6/30/72
PRINC INVEST: Dr. Murray Gardner, Department of Pathology
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Wade Parks, Bldg. 37, Room 1B22, x-65967
Dr. Victor Zeve, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Southern California, University of (72-2032)
ADDRESS : School of Medicine, 2035 Zonal Avenue, Los Angeles, California 90033
PHONE : AC-213, Phone 746-2121
CNTRCT TITLE: Conditioned Lethal Mutants of RNA Tumor Viruses (RSV)
DATES : 10/15/71 - 10/14/72
PRINC INVEST: Dr. Peter Vogt, Department of Microbiology
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. Stuart Aaronson, Bldg. 37, Room 2C07, x-66135
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Southwest Foundation for Research and Education (69-2011)
ADDRESS : P.O. Box 28147, 7480 West Commerce Street, San Antonio, Texas 78284
PHONE : AC-512, Phone 674-1410
CNTRCT TITLE: Housing and Maintenance of A Chimpanzee Breeding Colony
DATES : 4/25/72 - 4/24/73
PRINC INVEST: Dr. S.S. Kalter, Department of Virology
PROJ OFFICER: Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Southwest Foundation For Research and Education (71-2348)
ADDRESS : P.O. Box 28147, 7480 West Commerce Street, San Antonio, Texas 78284
PHONE : AC-512, Phone 674-1410
CNTRCT TITLE: Study of Latent Virus Infection and Transmission
DATES : 6/3/71 - 6/30/72
PRINC INVEST: Dr. S.S. Kalter, Department of Virology
PROJ OFFICER: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Stanford University (69-2053)
ADDRESS : Stanford, California 94305
PHONE : AC-415, Phone 321-2300 x-3435
CNTRCT TITLE: Procurement, Processing, Storage, Distribution and Study of Human Tumor Cell Cultures
DATES : 10/1/71 - 9/30/72
PRINC INVEST: Dr. Leonard Hayflick, Department of Medical Microbiology
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : St. Joseph's Hospital (69-2074)
ADDRESS : 3001 West Buffalo Avenue, Tampa, Florida 33607
PHONE : AC-813, Phone 877-8161, x-246
CNTRCT TITLE: Study on Human Sarcomas and Their Possible Viral Etiology
DATES : 6/24/71 - 6/23/72
PRINC INVEST: Dr. Jeno Szakacs
PROJ OFFICER: Dr. Albert Dalton, Bldg. 37, Room 1C16, x-64311
Dr. David M. Howell, Bldg. 37, Room 1D21, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : St. Jude's Children's Research Hospital (71-2134)
ADDRESS : 332 North Lauderdale, P.O. Box 318, Memphis, Tennessee 38101
PHONE : AC-901, Phone 525-8381
CNTRCT TITLE: Studies on The Etiology of Selected Amphibian Tumors
DATES : 5/13/72 - 4/30/73
PRINC INVEST: Dr. Allan Granoff
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Wilna Woods, Bldg. 37, Room 1D14, x-61478
SEGMENT : Developmental Research
SEG CHAIRMAN: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : St. Louis University (67-692)
ADDRESS : 3681 Park Avenue, St. Louis, Missouri 63110
PHONE : AC-314, Phone 865-2288, x-545
CNTRCT TITLE: Search For The Virus-Specific Genetic Material in Human Cancers--A Direct Test of The Viral Etiology of Human Cancer and Studies On The Mechanisms of Viral Oncogenesis
DATES : 3/20/72 - 3/19/73
PRINC INVEST: Dr. Maurice Green, Institute for Molecular Virology
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Tel Aviv University (72-3237)
ADDRESS : 155 Herzl Street, Tel Aviv, Aber-Kabir, Israel
PHONE :
CNTRCT TITLE: Isolation, Purification and Propagation of B-Type Particles From Human Milk in Israel
DATES : 3/22/72 - 11/1/73
PRINC INVEST: Dr. John Keydar
PROJ OFFICER: Dr. Timothy O'Connor, Bldg. 41, Room A105, x-63647
SEGMENT : Breast Cancer Virus
SEG CHAIRMAN: Dr. W. Ray Bryan, Federal Bldg., Room 4C08, x-64533
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Texas, University of (65-604)
ADDRESS : M.D. Anderson Hospital and Tumor Institute, 6723 Bertner Drive, Houston, Texas 77025
PHONE : AC-713, Phone 526-5411
CNTRCT TITLE: Studies On The Relationships of Viruses To Human Leukemia, Lymphomas and Solid Tumors
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Leon Dmochowski, Department of Virology
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
SEGMENT : Developmental Research
SEG CHAIRMan: Dr. Robert Manaker, Bldg. 37, Room 1B16, x-63323
CNTRCT SPEC : Mr. J. Thomas Lewin, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Texas, University of (71-2135)
ADDRESS : Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 73235
PHONE : AC-214, Phone 631-3220
CNTRCT TITLE: Biohazards Information Gathering Center: Surveillance of Laboratory-Acquired Infections and Accidents
DATES : 1/1/72 - 12/31/72
PRINC INVEST: Dr. S.E. Sulkin, Department of Microbiology
PROJ OFFICER: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
Mr. W. Emmett Barkley, Bldg. 41, Room A118, x-66981
SEGMENT : Biohazards Control and Containment
SEG CHAIRMAN: Dr. Alfred Hellman, Bldg. 41, Room A103, x-66758
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Texas, University of (71-2178)
ADDRESS : M.D. Anderson Hospital and Tumor Institute, 6723 Bertner Drive, Houston, Texas 77025
PHONE : AC-713, Phone 526-5411
CNTRCT TITLE: Immunological Treatment of Human Neoplastic Disease
DATES : 6/29/71 - 4/30/72
PRINC INVEST: Dr. Joseph G. Sinkovics, Department of Medicine
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
Dr. Ronald Herberman, Bldg. 10, Room 5B49, x-61366
Dr. Ernest Plata, Bldg. 41, Room 300, x-66178
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Texas, University of (72-3262)
ADDRESS : M.D. Anderson Hospital and Tumor Institute, 6723 Bertner Drive, Houston, Texas 77025
PHONE : AC-713, Phone 526-5411, x-546
CNTRCT TITLE: Human Immunity and Immune Response to The Rauscher Leukemia Virus
DATES : 5/24/72 - 5/23/73
PRINC INVEST: Dr. Evan Hersh
PROJ OFFICER: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : TRW, Inc. (70-2200)
ADDRESS : One Space Park, Redondo Beach, California 90278
PHONE : AC-213, Phone 679-8711
CNTRCT TITLE: Viral Antigens and Anti-Viral Antibody: Preparation, Purification and Properties
DATES : 1/1/72 - 12/31/72
PRINC INVEST: Dr. Norman Weliky
PROJ OFFICER: Dr. Vincent Hollis, Bldg. 41, Room A110, x-66178
Dr. Tibor Borsos, Bldg. 37, Room 2B15, x-63428
SEGMENT : Immuno-Epidemiology
SEG CHAIRMAN: Dr. Paul Levine, Federal Bldg., Room 5A12, x-66085
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : University Laboratories, Inc. (66-1133)
ADDRESS : 810 North Second Avenue, Highland Park, New Jersey 08904
PHONE : AC-201, Phone 246-1146
CNTRCT TITLE: The Production of Sarcoma Viruses, Helper Viruses and Antisera To These Viruses
DATES : 11/1/71 - 9/30/72
PRINC INVEST: Dr. Eugene Bernstein
PROJ OFFICER: Dr. Robert Holdenreid, Bldg. 41, Room A102, x-64333
Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Washington, University of (71-2171)
ADDRESS : Medical School, Seattle, Washington 98105
PHONE : AC-206, Phone 543-1448
CNTRCT TITLE: Studies on Tumor Specific Transplantation Antigen
DATES : 6/30/71 - 6/29/72
PRINC INVEST: Dr. Karl Hellstrom, Department of Pathology
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Washington, University of (72-2037)
ADDRESS : Office of Grant and Contract Services, Seattle, Washington 98195
PHONE : AC-206, Phone EA 5-8000, x-374
CNTRCT TITLE: Immunological and Transplantation Studies on Dogs With Cancer For Detection of An Oncogenic Virus-Carrier State
DATES : 11/1/71 - 10/31/72
PRINC INVEST: Dr. Rainer Storb, Department of Medicine
PROJ OFFICER: Dr. Gary Pearson, Bldg. 37, Room 1B05, x-62600
Dr. Wilna Woods, Bldg. 37, Room 1D14, x-61478
SEGMENT : Program Management
SEG CHAIRMAN: Dr. John B. Moloney, Bldg. 37, Room 1A13, x-61038
CNTRCT SPEC : Mr. Thomas Louden, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Weizmann Institute (69-2014)
ADDRESS : Rehovot, Israel
PHONE : 951-721
CNTRCT TITLE: Study on Virus-Induced Tumor Specific Transplantation Antigens
DATES : 4/22/72 - 10/21/72
PRINC INVEST: Dr. Leo Sachs, Section of Genetics
PROJ OFFICER: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Wisconsin, University of (72-2022)
ADDRESS : 750 University Avenue, Madison, Wisconsin 53706
PHONE : AC-608, Phone 262-1260
CNTRCT TITLE: Studies on The Roles of RNA Tumor Viruses and Related Genetic Information In The Induction of Tumors In Rodents By Chemicals
DATES : 9/1/71 - 8/31/72
PRINC INVEST: Dr. Charles Heidelberger
PROJ OFFICER: Dr. George Todaro, Federal Bldg., Room 502, x-66135
Dr. Roy Kinard, Federal Bldg., Room 504, x-66136
SEGMENT : Tumor Virus Detection
SEG CHAIRMAN: Dr. George Todaro, Federal Bldg., Room 504, x-66135
CNTRCT SPEC : Mr. Fred Shaw, Federal Bldg., Room B1C03, x-61521

CONTRACTOR : Wistar Institute of Anatomy and Biology (71-2092)
ADDRESS : 36th Street at Spruce, Philadelphia, Pennsylvania 19104
PHONE : AC-215, Phone 222-6700, x-226
CNTRCT TITLE: Extraction and Characterization of Virus-Induced Transplantation Antigen From Sarcomas and Leukemia
DATES : 2/1/72 - 1/31/73
PRINC INVEST: Dr. Anthony Girardi
PROJ OFFICER: Dr. James T. Duff, Bldg. 37, Room 1B22, x-65967

SEGMENT : Solid Tumor-Virus
SEG CHAIRMAN: Dr. Robert Huebner, Bldg. 37, Room 2D24, x-63301
CNTRCT SPEC : Mr. Thomas Porter, Bldg. 37, Room 1A03, x-65025

CONTRACTOR : Wolf Research and Development Corporation (71-2270)
ADDRESS : 6801 Kenilworth Avenue, Riverdale, Maryland 20840
PHONE : AC-301, Phone 779-2800
CNTRCT TITLE: Data Processing Support For Biomathematical and Biomedical Research
DATES : 9/15/71 - 8/31/72
PRINC INVEST: Dr. William Wells
PROJ OFFICER: Dr. Deward Waggoner, Federal Bldg., Room 5A08, x-64148
Mr. Theodore Weiss, Federal Bldg., Room 612B, x-61606
SEGMENT : Program Resources and Logistics
SEG CHAIRMAN: Dr. Jack Gruber, Bldg. 37, Room 1D15, x-61718
CNTRCT SPEC : Mr. Charles Fafard, Bldg. 37, Room 1A03, x-65025