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RESEARCH EDUCATION CONTROL

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ANTICANCER VACCINE TRIALS DUE IN THREE-FOUR YEARS; VIRUS RESEARCH OPPORTUNITIES DESCRIBED

NCI's Virus Cancer Program has moved into a new era, partly as the result of changes recommended in the Zinder Report, partly as the consequence of evolving leadership capabilities and changes in scientific emphasis and opportunities.

This new era will bring, within three to four years, development of

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In Brief

SCHMIDT HAS DOUBTS ABOUT COMMUNITY SATURATION PROGRAM; DIANE FINK WINS GERARD LAMBERT AWARD

CANCER RESEARCH Emphasis Grants, NCI's new funding mechanism, was adopted with extremely good intentions, Panel Chairman Benno Schmidt commented recently. "But it needs close watching. The scientific community could get the notion, 'My god, now they're targeting grants'." . . . **SCHMIDT TOOK** exception to the *New York Times'* comparison of the National Cancer Program with the Vietnam War, inferring in both that there was an "ever elusive light at the end of the tunnel." "The parallel excapes me," Schmidt said. "Our war with cancer is not 12,000 miles away; there is no opportunity for withdrawal; and we either fight this one or surrender." . . . ***CANCER THERAPY ABSTRACTS***, Vol. 16, No. 1, will be published in August by the Franklin Institute Press. Price is $45 domestic, $55 foreign. It will cover publications on chemotherapy, cancer related surgery, radiotherapy and immunotherapy. Computer tapes also will be available in August for an additional fee. Contact the publisher, Benjamin Franklin Parkway, Philadelphia 19103. . . . **DIANE FINK**, director of NCI's Div. of Cancer Control & Rehabilitation, has received the Gerard Lambert award for the efforts of her division in fostering continuing education of physicians and hospital staffs in communities where there are no large medical centers. . . . **SCHMIDT WAS** critical of Cancer Control's community-based saturation program, questioning Fink at length about it at the July panel meeting. Schmidt fears that, as demonstration projects designed to show how cancer care can be improved through the cooperative efforts of community organizations, they will be ignored by communities where intense rivalries prevent that kind of cooperation. Schmidt also implied a lack of confidence in the DCC&R Advisory Committee, suggesting that "it might be useful to add (to the committee) a couple of people proven over the years, people wise and experienced." He backed off when Fink named the professional members—Chairman Gerald Murphy, Michael Shimkin, Charlene Holton, Ann Pettigrew, George Rosemond, William Powers, Arthur Holleb—and agreed that they were indeed competent and experienced. The terms of Holleb, Powers, Rosemond and Shimkin expired June 30, along with that of lay member Louis Fink.

NEW RESEARCH AREAS IN VIRUS PROGRAM DESCRIBED; INTRAMURAL CHANGES MADE

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an anticancer vaccine to the clinical testing stage, according to John Moloney, associate director for viral oncology. "We'll know within a year after the start of field tests if it works," Moloney told *The Cancer Letter.*

Most likely candidates for the early clinical trials will be vaccines for leukemias and sarcomas, Moloney said.

The fact that vaccine development now has a tentative target date does not mean VCP has dropped its broad-based, long range research plan for the identification and control of virus-induced cancers of man. An outline of the program's broad categories of studies along with possible new research areas follows.

Virus (or Virus Expression)–Tumor Relationships

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, since these agents may provide the best probes for detection of type C virus information in human cells. This work will remain an integral part of the program.

Human studies. Efforts to identify viruses or detect virus expression in human tumors have been underway for some time. The program will continue to increase its activities in the search for viruses which induce malignancies in man:

- To identify and isolate candidate viruses or subviral products in leukemias, lymphomas, sarcomas and carcinomas.
- To identify and isolate candidate viruses or subviral products in lung, colon and other carcinomas.
- To develop methods for the detection of high cancer risk groups, i.e. individual susceptibility or predisposition to transformation by human viruses.
- To extend existing and develop new methods to induce tumor virus expression in "normal" cells.
- To develop suitable reagents and to improve existing immunological and biochemical methods for mass diagnostic screening for candidate viruses.
- To characterize, biologically and biochemically, presumptive human virus isolates.
- To increase emphasis on understanding the relationship of environmental agents (e.g. chemical carcinogens) as co-factors in viral carcinogenesis.

Molecular Studies

Major progress in the understanding of the molecular pathways of tumor virus replication has been made within the past year. Such advances 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 RDDP. 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.

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.

Applied studies. As knowledge of the fundamental molecular events in virus-cell interaction increases, the program will continue to apply this information to the study of human cancer as follows:

- To identify and characterize similar enzymes or enzymatic activities within normal and malignant human cells.
- To develop highly sensitive methods for the detection of virus or virus activity in human cells.
- 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.

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.

Basic studies. Investigations of selected model systems, representing tumors induced by type C, type B and herpesviruses, 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. Research on spontaneous or naturally occurring tumors in model systems relevant to human cancer will be continued as a basis for a rational approach to prevention and treatment:

- To study cellular and humoral immune mechanisms and to determine their relative significance in host recognition of and response to virus-induced

tumors and/or tumor viruses.

• To develop methods to enhance host response to virus-induced tumors or tumor virus antigens.

Applied studies. As basic research provides the framework for identification and characterization of viruses, viral antigens, and virus-induced cell membrane alterations in human cancers, immunological methods will be applied:

• To relate candidate human viruses to known oncogenic agents.

• To identify and characterize intra- and interspecies viral antigens which are present in known mammalian tumors as probes for detecting human tumor viruses or viral antigens.

• To determine the presence of crossreacting antigens implying viral causation in various human tumors.

• To launch large-scale seroepidemiological surveys which will define populations at high risk to virus-induced cancers.

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

• Development of vaccines (viral or subviral components) from identified and fully characterized human tumor viruses.

• Determination of the role of host immune responses in virus-induced tumor recognition and rejection.

• Application of basic and applied studies in the prevention and control of human cancer.

Test Systems and Resources

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

• To determine the oncogenic potential of candidate human viruses.

• To develop bioassay systems for testing viral and viral/chemical carcinogens.

• To begin viral vaccine (conventional or other) testing and immunization programs.

• To begin viral therapy testing programs.

• To explore special animal tumor systems, especially in primate species particularly relevant to human cancer.

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

Many of these systems are being developed at the Frederick Cancer Research Center.

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:

• Human resources. Collection and storage of serum and tissue specimens; integration of data on clinical records, storage and distrubition; computerization of specimen collection.

• Animal models. Maintenance of various mammalian animal colonies for basic research and special studies.

• 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.

• Candidate human virus production. Intensive developmental research effort to isolate and produce human viruses.

• 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.

Moloney has implemented major changes in the intramural structure of his organization. Previously, he had three branches headed by key figures in the VCP—Viral Biology, with Robert Manaker as chief; Viral Carcinogenesis, headed by Robert Huebner; and Viral Leukemia and Lymphoma, headed by George Todaro.

Those branches are gone, and in their place are:

★ Laboratory of Tumor Virus Genetics, headed by Edward Scolnick, who previously was head of the Genetics Section in Todaro's branch. Wade Parks is the assistant chief of the new lab; he was formerly head of the Viral Genetics Section in Huebner's branch.

★ Laboratory of RNA Tumor Viruses, with Huebner as chief and Stuart Aaronson and Michael Chirigos as assistants. Aaronson was head of the Solid Tumor Virus Section in Huebner's branch while Chirigos was head of the Virus and Disease Modification Section in Manaker's branch.

★ Laboratory of Viral Carcinogenesis, with Todaro as chief and Peter Fischinger and Tadao Aoki as assistants. Fischinger headed the Tumor Virus Section and Aoki the Immunology Section in Todaro's branch.

★ Collaborative Research Branch, headed by Manaker with James Duff as assistant.

★ Laboratory of DNA Tumor Viruses. Manaker is acting chief while Moloney is recruiting "a senior individual" to head the lab. Berge Hampar, formerly head of the Solid Tumor Virus Section in Huebner's branch, is assistant.

The new Collaborative Research Branch will be primarily responsible for administering VCP contracts. Contracts currently in established segments will be redistributed among newly created sections according to the general scope of the work.

Moloney said the changes were needed to provide new opportunities for inhouse scientists who deserve and want more responsibility; attract new scientists and program leaders; take cognizance of the changes in scientific emphasis and opportunities and maintain high productivity among scientific personnel; and effect a separation in the operations of the intramural and collaborative (contract) research programs.

For the first time, VCP has an advisory committee to advise NCI on broad directions for the program. Frank Putnam, Univ. of Indiana, is chairman. Other members are Emil Frei III, Children's Cancer Research Foundation, Boston; Charlotte Friend, Mt. Sinai; Daniel Nathans, Johns Hopkins; Lloyd Old, Sloan-Kettering; William Robinson, Stanford; and Robert Wagner, Univ. of Virginia.

Among the committee's responsibilities, particular emphasis will be placed on allocation of resources, areas for expanded research and development, and the application of research findings to the control of cancer in man.

The advisory committee will not be involved in the review and approval of individual contracts, the job reserved for the two Scientific Review Committees which were chartered and went to work during the 1975 fiscal year.

Moloney does not feel the new review process will add further delays to the already lengthy contract implementation process.

One of the harshest criticisms of VCP as it was operated until this year was that the practice of using contractors as extensions of intramural research, with the contract process as it was then not subject to the intensive peer review accorded grants, led to the award of contracts to "cronies," friends and others with inside information or contacts.

"I personally don't think that existed, although I understand how it could appear to be so," Moloney said.

As a result of the new policy to offer VCP RFPs to a broader segment of the scientific community, there is more competition, "more exposure of the program to the kind of science we want," Moloney said. Another result: acceptance of fewer unsolicited proposals.

VCP scientific activities, including some of the major developments in the field of tumor biology during the past year, were covered in the report submitted to the National Cancer Advisory Board by its subcommittee on Implementation of the Zinder Recommendations. The report on those activities follows:

RNA Viruses

Oncogenic RNA viruses belong to a class of RNA viruses distinguished by having an RNA-directed DNA polymerase (RDDP). At present, two major groups are recognized: (1) type C viruses and (2) type B viruses. The two groups, differentiated by their morphology and the diseases they cause, appear to show no crossreaction by immunologic and nucleic acid hybridization techniques. Viruses of both groups (1) mature by budding through the cell membrane, (2) have a density of 1.15-1.19 in sucrose gradients, (3) have 70S RNA as their genome, and (4) contain RDDP. Besides the two major groups, a few viruses have been identified that seem to fall somewhere between type C and type B viruses in their morphologic characteristics, e.g., Mason-Pfizer Monkey Virus (MPMV) and guinea pig endogenous virus.

Type C viruses. These generally fall into two classes—leukemia and sarcoma viruses. Both occur in a wide variety of species in which they cause leukemias, lymphomas and related neoplasms. Although all leukemia viruses can infect, replicate and mature independently, most mammalian sarcoma viruses are defective. The latter can transform cells which they infect but cannot replicate except in the presence of a helper leukemia virus. The leukemia virus supplies the functions lacking in the sarcoma virus but does not itself have the ability to transform cells. Many leukemia and sarcoma stocks are probably mixtures or recombinants of several viruses. Recent experiments have demonstrated that the various type C viruses recombine readily and that RNA from one type can be packaged in a coat of another type. It appears plausible that a transforming virus could be formed when a non-oncogenic virus picks up "transforming information" either from its host or from virus integrated into the host genome.

Type B viruses. The most extensively studied type B virus is the Mouse Mammary Tumor Virus (MMTV) which causes mammary adenocarcinoma in mice. Characterization of this virus has lagged behind that of type C viruses because of the lack, until recently, of a system for large-scale growth of the virus in cell culture. Since it has recently become possible to grow MMTV to higher titer, great strides have been made in studies of the virus. A hormone, dexamethasone, has a strong stimulatory effect on viral replication. The hormone appears to increase the rate of transcription as measured by viral RNA synthesis. This is the only known case where a hormone has been shown to stimulate preferentially transcription of a specific RNA.

(The rest of this report on VCP scientific activities will appear in subsequent issues of ***The Cancer Letter****)*

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

(The following RFP was announced by the National Institute of Environmental Health Sciences)

RFP NIH-NIEHS-76-1

Title: *Species-to-species carcinogenesis extrapolation*
Deadline: *Sept. 29*

The National Institute of Environmental Health

Sciences is interested in the establishment and award of a research contract to create a data summary from published studies in the field of carcinogenesis and to utilize this data summary to investigate various aspects of the quantification of species differences following exposure to specified carcinogenic agents such as:

(1) The most appropriate dosage metric for establishing species equivalency.

(2) Dose-response relationships within and across species.

It is estimated that the project will require one year with 18 man-months effort for completion. Prospective solicitors should have expertise in cancer research, biostatistics, and pathology.

Contract Specialist: Fred Suggs
Research Contracts Branch
Div. of Contracts & Grants
NIH, Bldg 31, Rm 1B32
Bethesda, Md. 20014
301-496-4487

NEW REPORT ON 1960-71 SURVIVAL TRENDS NOW AVAILABLE FROM NCI

NCI has released a report on survival trends among white cancer patients diagnosed between 1960 and 1971 in approximately 100 U.S. hospitals.

NCI scientists found that survival has improved for some cancers, while remaining essentially unchanged for others.

The study measured trends in survival for 48 types of cancer from the 1950's to the 1960's with provisional one-year data on patients diagnosed in the early 1970's.

Data for the report, entitled "Recent Trends in Survival of Cancer Patients 1960-1971," were provided by a group of cancer registries, which have monitored an estimated 10% of cancer patients in the U.S. since the 1940's. The report was edited by Lillian Axtell and Max Myers of NCI's End Results Section.

One-year, three-year, and five-year survival rates were reported for 230,502 patients who were diagnosed between 1960-64 and 1965-69. One-year provisional survival rates were provided for 45,443 patients diagnosed in 1970-71.

The hospitals in the study included all hospitals in Connecticut, hospitals which treated approximately one-third of the cancer cases diagnosed in California, several hospitals in the Boston metropolitan area, and six large university hospitals in various parts of the U.S.

Patients with cancers of the prostate, testis, kidney, bladder, brain, thyroid, larynx and melanoma of the skin diagnosed during the late 1960's experienced more favorable survival than those diagnosed during the 1950's or early 1960's.

Among women with breast cancer, five-year survival increased from 60% in the 1950's to 64% in the late 1960's, reflecting the increased proportion of women diagnosed during 1965-69 with localized disease.

For male patients with Hodgkin's disease, five-year survival improved from 31% in the 1950's to 38% during 1960-64 and 52% during 1965-69. The pattern was similar for women.

One-year survival for children with acute leukemia improved markedly during the 1960's, and provisional results for children diagnosed in 1970-71 suggest that this upward trend is continuing. However, five-year survival has progressed at a much slower pace in this study.

Among patients with lymphosarcoma or reticulum cell sarcoma—forms of non-Hodgkin's lymphoma—little change in survival was evident except for patients diagnosed in 1970-71, whose one-year provisional survival rates suggested that the five-year rates will improve during the 1970's.

"Recent Trends in Survival of Cancer Patients 1960-71" supplements the 1972 NCI report, "End Results in Cancer Report No. 4," which analyzed survival of white cancer patients diagnosed 1940 through 1969. In the earlier report, five-year survival was not available on patients diagnosed during 1965-69.

Single copies of the new report are available free from the Office of Cancer Communications, NCI, Bethesda, Md. 20014.

SEVENTEEN NEW ACS—ELEANOR ROOSEVELT GRANTS AWARDED TOTALING $271,613

Seventeen American Cancer Society—Eleanor Roosevelt International Cancer Fellowship grants have been awarded totaling $271,613.

The awards have been made annually since 1961; they enable foreign scientists to pursue significant research in the U.S. and other countries, while American investigators are enabled to work abroad. Recipients work with scientists in specialized institutions for a year. In order to qualify for such grants an investigator must be able to return to a post in his home institution to continue research, assume some teaching responsibilities and in general share with his colleagues the benefits of his year abroad.

The 1975-76 awards will permit scientists from California, Florida, Illinois, Hawaii and Pennsylvania to work abroad and others from Australia, Ghana, Great Britain, Israel, Sweden, and Switzerland to work here. Additionally a Japanese scientist will work in England and another in France; a Bulgarian will go to England; and a French investigator will go to Switzerland. Their grants range from $2,179 to $30,304 and include travel expenses for the fellows and their dependents. Two of the 17 grantees are women.

The Fellowship program is financed by the ACS and administered by the International Union Against Cancer. The program facilitates worldwide exchange

as well as an opportunity for uninterrupted research in an environment free from the ordinary daily responsibilities.

The new group of 17 fellows brings the total number of scientists served by the program to 279 since 1961.

The 1975-76 fellows are:

Derek Burke, England, to Univ. of Colorado; Wayne Criss, Univ. of Florida, to Kobe Univ., Japan; Dino Dina, Switzerland, to Univ. of California (Berkeley); Floyd Dunn, Univ. of Illinois, to Institute of Cancer Research, Surrey, England; Brigitte Huber, England, to Harvard Medical School; David J. Kemp, Australia, to Stanford Univ.; Toshio Kuroki, Japan, to International Agency for Research on Cancer, Lyon; Philip Loh, Univ. of Hawaii, to Univ. of Bristol, England.

Francis Nkrumah, Ghana, to NCI; Francois Rougeon, France, to Univ. of Geneva, Switzerland; Stanley Schrier, Stanford Univ., to Univ. of Oxford, England;

Toyozo Sekiguchi, Japan, to Sir William Dunn School of Pathology, Oxford, England; Geoffrey Shellam, England, to NCI; Rabi Simantov, Israel, to Johns Hopkins Univ.; Morag Timbury, Scotland, to Baylor College of Medicine; Dimitar Todorov, Bulgaria, to Chester Beatty Research Institute, London, and William Weidanz, Hahnemann Medical College, to Copenhagen.

NCI ADVISORY GROUP MEETINGS FOR AUGUST

Virus Cancer Program Scientific Review Committee B—Aug. 4, Bldg 37 Room 1B04, open 9—9:30 a.m.

Carcinogenesis Program Scientific Review Committee—Aug. 4-5, Landow Bldg Room B301, open Aug. 4, 9—10 a.m.

President's Cancer Panel—Aug. 13, Bldg 31 Room 8, open 9:30 a.m.—noon, and 2 p.m.—adjournment.

Diet, Nutrition & Cancer Program Advisory Committee—Aug. 19-20, Bldg 31, Room 7, all open both days from 9 a.m.

Interagency Coordinating Committee for Cancer Control & Rehabilitation—Aug. 20, Bldg 31 Room 8, open 9 a.m.—5 p.m.

Committee on Cancer Immunotherapy—Aug. 28, Bldg 10 Room 4B17, open 1—1:30 p.m.

Contract Awards

MARYLAND $4.7 MILLION CONTRACT LEADS OFF NEW FISCAL YEAR AWARDS

First major contract awarded in the 1976 fiscal year by NCI was to the Univ. of Maryland University Hospital, totaling $4,653,700. It was for continuation of the university's performance of medical and laboratory services at the Baltimore Cancer Research Center, in Div. of Cancer Treatment programs involving combined modalities treatment of cancer patients.

Other awards:

Title: Studies of alteration in translation of genetic messages induced by viruses and carcinogenesis
Contractor: Weizmann Institute of Science, Rehovot, Israel, $314,000.

Title: Immunochemotherapy research
Contractor: State Univ. of New York, $134,301.

Title: Significance of mutagenesis in carcinogenesis
Contractor: Johns Hopkins Univ., $101,875.

Title: Study on the relationship of fetoglobulins to the induction of hepatomas by chemical carcinogens
Contractor: Univ. of California (San Diego), $482,457.

Title: Studies and investigations on therapy of patients with Stage II and Stage III carcinoma of the breast
Contractor: Evanston Hospital, Evanston, Ill., $170,000.

Title: Therapy of patients with pancreatic carcinoma
Contractors: Mayo Foundation, $203,841; New York State Dept. of Health, $207,376.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for information purposes only. RFPs are not available.

Title: Clinical data reduction services
Contractor: Automation Industries Inc.

Title: Epidemiologic studies in the etiology of cancer in veterans
Contractor: National Academy of Sciences

Title: Cancer End Results evaluation
Contractor: Connecticut State Dept. of Health

Title: Retrospective case control study of reserpine and breast cancer
Contractor: University City Science Center

Title: Study of cancer in Japanese atomic bomb survivors
Contractor: National Academy of Sciences

Title: Studies of Marek's disease as a model of human herpesvirus oncogenesis
Contractor: Life Sciences Inc.

Title: Organ culture assay of vitamin A analogs
Contractor: Southern Research Institute

Title: Microsomal enzyme studies
Contractor: Microbiological Associates

Title: Production and maintenance of germ-free animals
Contractor: Life Sciences Inc.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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