THE CANCER LETTER
RESEARCH EDUCATION CONTROL

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NCI COMMUNICATIONS EFFORT, SAVED BY CONGRESS, NOW A MAJOR NATIONAL CANCER PROGRAM RESOURCE

NCI's office of Cancer Communications has assumed a major role in the National Cancer Program, as the result of the demands of the program and a specific congressional mandate that is unique among federal agency information offices.

Congressional and public proponents of the cancer program were concerned from the start about "technology transfer" – passing on the results of cancer research to the public and medical profession as quickly as possible. The National Cancer Act of 1971 included a provision authorizing NCI to "collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer."

Efforts to implement that provision were hampered by the Nixon Administration's cutbacks of HEW information activities. When Con-

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In Brief

CANCER CONTROL WORKING ON NEW REVIEW GUIDELINES; PRESIDENT ASKS CONGRESS FOR CIGARETTE REGULATION

NEW REVIEW guidelines for contract proposals in NCI's Div. of Cancer Control & Rehabilitation are being developed, probably will be implemented next month. No major changes are expected. . . . **CONGRESS SENT** President Ford a message with the thumping override of his veto of the nurses training, health revenue sharing and health services bill. It could soften him somewhat when he gets the HEW appropriations and National Research Service renewal bills. . . . **PRESIDENT FORD** astounded some members of the National Cancer Advisory Board when he passed on to Congress the Board's recommendation for federal control of high tar and nicotine cigarettes. After the Board had responded to the President's request for scientific evidence of the harmful effects of cigarettes (*The Cancer Newsletter*, Nov. 29, 1974), there was nothing but silence from the White House. NCAB members felt the President did not want to stir up tobacco-state opposition and would let the matter die. But the Administration's annual report to Congress on smoking and health asked for legislation to regulate tar and nicotine content of cigarettes–exactly what NCAB had proposed to Ford. . . . **ROBERT STONE**, fired earlier this year as NIH director, has been appointed dean of the Univ. of Oregon School of Medicine. . . . **PERSONNEL CHANGES**–John Ziegler, who has been chief of the Pediatric Oncology Branch at NCI, has been named deputy clinical director. Vincent DeVita, director of the Div. of Cancer Treatment, will serve as clinical director until he finds someone to fill the job, vacated by George Canellos, who went to the Sidney Farber Center. Arthur Levine is acting chief of the Pediatric Oncology Branch. Robert Young has been appointed chief of the Medicine Branch; he'll continue as head of the Cellular Kinetics section.

COMMUNICATIONS OFFICES ESTABLISHED AT EACH COMPREHENSIVE CANCER CENTER

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gress renewed the Act in 1974, the House report on the bill noted that "NCI has been prevented from conducting a full range of communications, information and public affairs activities in support of the National Cancer Program because of the centralization of the responsibility to conduct these activities in NIH and HEW and accompanying 25% reduction in NCI public affairs personnel . . . NCI has inadequate resources and is doing an inadequate job of sharing with the research, professional and public communities the results and discoveries of the cancer program which could be used to improve the prevention, treatment and rehabilitation of cancer.

"For these reasons, the legislation includes specific authority for the director of NCI to engage in the dissemination and interpretation of new and existing knowledge and information produced by the cancer program to the concerned communities, including researchers, practicing physicians and the general public. . . . This authority and its exercise by NCI should not be restricted or curtailed by HEW. . . . Since these activities are crucial to the program and appropriate for it, it is intended that this limitation and interference by HEW will be stopped."

In the year since this language removed those restructions, NCI has moved quickly to carry out the mandate, under the leadership of Paul Van Nevel, associate director for cancer communications. OCC's budget went from $1 million to $2.4 million, and it is in the process of carrying out or implementing these programs:

• Communications offices are being established in each of the 17 comprehensive cancer centers. These offices will develop data for responding to physician and public inquiries. Each center will have a toll free phone number to handle these inquiries, and a back-up toll free number will be installed at OCC to enable centers to refer difficult calls to NCI. This program with the centers is being funded through three-year contracts averaging $80,000 a year each (with the money coming out of the Div. of Cancer Control & Rehabilitation budget, not OCC's).

NCI hopes that the entire nation can be covered with the 17 offices. If some sections cannot be included in one of the toll free areas, additional contracts will be awarded specifically to fill in the gaps. Additional comprehensive cancer centers that will be added later probably will not participate in this program. NCI does not expect to fund this program past the initial three years; centers are required to bring other organizations into their outreach efforts, to help finance them when NCI support ends.

OCC has assigned a cancer control communications unit to DCCR to assist in identifying communications components of demonstration and other cancer control projects; to serve as a resource in support of identified communications needs; and to help establish a national cancer education program. This unit is headed by Elaine Bratic.

• Institutional liaison and special communication projects are handled by the Program Liaison Branch under Robert Schonfeld. Liaison efforts with cancer centers, research institutions, medical schools, state health departments, hospitals and voluntary agencies are aimed at informing them of services available through NIH and NCI, and assisting with communications, management, planning, and developing outreach activities.

Special communications projects include the "special communication of the director" – targeted mailing lists which selectively receive letters on research or treatment topics. The branch is expanding these categories so that NCI can reach an audience with timely information within 48 hours.

Special projects also deals with attempts to develop new ways, as well as evaluate and best utilize existing methods, of communicating with the medical and scientific communities and the public.

Other projects of the branch include development of an internal NCI communications program; helping centers produce individual newsletters; assist with six media symposia a year; managing a speakers and TV appearance bureau; and preparation of exhibits for professional society meetings and lay audiences describing the research and management activities of NCI and the cancer program.

• Tracking of scientific and programatic activities of the National Cancer Program and answering inquiries from patients, physicians, health organizations and the press are tasks handled by the Education & Technical Reports Branch, headed by William Gray. The tracking function is handled by a staff of five science writers.

This branch prepares and updates pamphlets about specific cancers for use by the public, patients and medical community. It is in the process of developing an entire new series of better designed pamphlets, including one or more new ones on psychological aspects of rehabilitation, in cooperation with the American Cancer Society.

The public inquiries section of the branch answered 21,950 inquiries in fiscal 1975, with the assistance of an outside contractor, Biospherics Inc., Rockville, Md.

"Public inquiries come from doctors, Congressmen, reports and, perhaps most importantly, patients, their friends and relatives," Gray told the National Cancer Advisory Board. "Helping these people is clearly a mandate of Congress. Far more importantly, it is a human mandate of the highest priority.

"Many of these are sick, weary and scared, and it has been our experience that frequently they do not want specific information as much as they want somebody just to listen sympathetically. For this reason

we must continue to answer their calls personally and sympathetically.

"We do not refer patients, but we do inform them of appropriate NCI supported institutions within their geographic area, which they may wish to discuss with their physicians."

• Development of a clearinghouse for cancer information is one of the tasks undertaken in a new contract awarded to a consortium of three firms—an agency, Buffington/Mingo Associates, Porter, Novelli & Associates Inc., and Kappa Systems Inc. The contractors are in the process of collecting information on a wide variety of information pieces—pamphlets, books, films, exhibits—from all possible sources. The job will include evaluating them for effectiveness and determining if any areas are not covered and if any are covered too heavily.

Other tasks to be handled by the consortium include providing technical assistance for the national communications network, developing messages and materials for a variety of public audiences, helping NCI initiate communication and education activities with private and public organizations, pretesting communications programs, and assisting in communications with health professionals.

Despite the 140% increase in budget over two years, OCC's staff has grown only from 25 to 29. This does not include six persons "on loan" from various universities and other institutions. The "loaners" are in a program in which they work at NCI for a year while remaining on their home institution payrolls. NCI reimburses the institutions, and the "loaners" are not counted against NCI's personnel ceiling.

Van Nevel pointed out other aspects of OCC's program in his presentation to NCAB:

* The American Cancer Society staff works closely with OCC to assure that communications programs of NCI, ACS, and the centers are conducted in a way that is nonduplicative, supportive, "and hopefully, synergistic," Van Nevel said. "Obviously, this communications activity must be coordinated with many other organizations as well."

* A new effort has been made to keep the scientific and professional communities informed of NCI activities. During the past year, staff member Norma Golumbic has produced 14 documents; much of her work appears under Director Frank Rauscher's byline in scientific journals.

* Since OCC has had difficulty finding qualified persons for its various specialized jobs, it is starting a communications internship.

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.

RFP NO1-CO-65325-04

Title: *Statistical analysis and quality control center for the centralized cancer patient data system (CCPDS)*

Deadline: *About Oct. 1*

A centralized cancer patient data system is to be developed, implemented and operated that encompasses selected personal and clinical data including a coded description of the cancer (or cancers) from patients seen and followed up initially by the comprehensive cancer centers in the United States.

Operation of the system shall include collection and storage of the data in a standard format, quality control mechanisms, evaluation of the data according to statistical needs of NCI and the centers and the issuance of standard and special reports to NCI and to the centers.

Contract Specialist: Pat Eigler
Control & Rehabilitation
301-427-7984

CONTRACT AWARDS

Title: Phase I – Planning for a community based cancer control program

Contractors: Connecticut State Dept. of Health, $160,309; and American Cancer Society, California Div. Inc., $110,724.

Title: Early detection, localization, and therapy of lung cancer

Contractor: The Johns Hopkins Univ., $350,000.

Title: Development and application of methods of N-nitroso compounds

Contractor: Thermo Electron Corp., Waltham, Mass., $99,885.

Title: Development and testing of a system to improve x-ray imaging, contrast and sharpness by elimination of scatter, while retaining the resolution of film

Contractors: Univ. of Wisconsin, $199,084; and Univ. of Alabama, $90,078.

Title: Design of an experiment to assess the impact of multi-site screening on total cancer mortality

Contractors: Univ. of Tennessee, $104,110; and Univ. of Minnesota, $69,212.

Title: Use of screening technique for blood in the stool as a means of detecting early cancer of the bowel

Contractor: Univ. of Minnesota, $308,437.

Title: Development of detailed methods and protocols for carcinogenesis screening using cell culture assays, Task V
Contractor: The Children's Hospital of Akron, $603,456.

Title: Operation and maintenance of biological data processing system
Contractor: Value Engineering Co., Alexandria, Va., $149,787.

Title: Preclinical canine bone marrow transplantation and immunotherapy studies
Contractor: Hazleton Laboratories, $408,580.

Title: Demonstration project on the earlier detection of breast cancer
Contractor: Iowa Lutheran Hospital, Des Moines, $173,080.

Title: Immunological, enzymatic and other biochemical markers for detection of abnormal cervical cells on slides or in suspensions by optical methods
Contractor: Polysciences, Inc., Warrington, Pa., $139,896.

Title: Studies and investigations on the diagnostic value of gynecologic cytopathology samples
Contractor: Univ. of Chicago, $62,500.

Title: Develop methods for detecting pancreatic cancer at an early or small stage and prior to the presence of metastasis
Contractor: Univ. of Chicago, $169,194.

Title: Studies for usefulness of carcinoembryonic antigen in diagnosis of bowel carcinoma
Contractor: Mayo Foundation, $187,573.

Title: Survey of exposure to chemical carcinogens and recommended control and intervention programs
Contractor: Stanford Research Institute, $1,598,530.

Title: Prototype network demonstration in head and neck cancer
Contractor: Northern California Cancer Program of Palo Alto, $199,000.

Title: Psychological aspects of breast cancer
Contractor: Stanford Research Institute, $253,305.

Title: Evaluation of thermography in mass screening for breast cancer
Contractor: Jefferson Medical College, $997,400.

Title: Data Management center for the breast cancer demonstration projects
Contractor: University City Science Center, Philadelphia, $886,826.

Title: Study of structural properties of cancer therapuetic agents
Contractor: Pomona College, $43,800.

Title: Exploration of the use of a proton beam in tissue densitometry
Contractor: Univ. of Chicago, $84,079.

Title: Vaginal-cervical cell sample sources for cytology automation
Contractor: State Univ. of New York, $25,511.

Title: Study the nature of interactions between tumor cells and immunoglobins
Contractor: Tel-Aviv Univ., $52,958.

Title: Chemical characterization of purified thymic products or other agents promoting lymphocyte differentiation
Contractor: New York Univ. Medical Center, $101,233.

SOLE SOURCE NEGOTIATIONS

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

Title: Establish tissue culture lines from patients with breast cancer
Contractor: M.D. Anderson

Title: Detroit SSMA Population-based Cancer Registry
Contractor: Michigan Cancer Foundation

Title: Evaluation of thermography in mass screening for breast cancer
Contractor: Health Insurance Plan of Greater New York

Title: Supramolecular organization of normal and tumor cell surfaces and their relationship to escape from immune surveillance and growth control
Contractor: Salk Institute

Title: Acquisition of gibbon primates for breeding and research purposes
Contractor: New Jersey Research Foundation for Mental Hygiene

Title: Environmental control system
Contractor: RP Industries Inc., Hudson, Mass.

Title: Isolation and tissue culture of human tumor cells
Contractor: Sloan-Kettering Institute

VIRUS CANCER PROGRAM REPORT ON SCIENTIFIC ACTIVITIES CONTINUES

The report on scientific activities of the Virus Cancer Program continues. The report last week included a discussion of DNA viruses; that discussion continues, followed by suggestions for development of treatment and control methods.

Herpes Simplex Virus. Carcinoma of the uterine cervix is now clearly recognized as the second most common malignant disease of women in the United States. Epidemiologic studies provided the first suggestive evidence that an infectious, venereally transmitted agent was associated with this disease. Later cytohistopathologic, virologic, and seroepidemiologic studies confirmed this observation and identified the

suspect agent as Herpes simplex virus type 2 (HSV-2). It is now clear that squamous cell carcinoma of the cervix is related to sexual activity. The pivotal demographic and epidemiologic characteristics that distinguish women at greater risk to developing cervical cancer are low socioeconomic status, early age at first coitus, and number of sex partners.

Seroepidemiologic studies have provided the strongest evidence associating HSV-2 with cervical cancer. Generally, antibodies to HSV-2 have been found more frequently and in higher titer among women with cervical cancer than among control women of similar age, race and socioeconomic level. The antibody activity was found to be age-dependent among control women but not among women with cancer, suggesting that women in the latter group are infected by HSV-2 earlier in life. These differences between patients with cervical carcinoma and controls are more impressive in black than in Caucasian women and in the U.S., Belgium, and Denmark than in Israel, Columbia, and New Zealand. The occurrence of antibodies to HSV-2 has been noted to increase with progression of the disease; the lowest incidences were found among women with dysplasia and the highest among women with invasive cancer.

Some inconsistencies have been observed in the seroepidemiologic studies and may, in part, be related to shortcomings in the serological specificity of the tests employed. The accuracy with which the present assay methods detect past infections with HSV-2 is unknown. Herpes simplex virus types 1 and 2 appear to share common antigens and have one or more type-specific antigens. Infection with either virus results in the production of antibodies that will crossreact with heterotypic virus. A prior infection with HSV-1 modifies the production of antibodies to HSV-2 while an infection with HSV-2 in an individual previously infected with type 1 virus may stimulate an anamnestic response to the shared antigens of the two viruses. Thus, the criteria used for assessing positivity or negativity for antibodies to HSV-2 may not adequately depict the status of a past infection with this virus. Clearly, the isolation, purification, and characterization of HSV type-specific antigens is crucial to definitive seroepidemiologic studies.

HSV-2 nonvirion antigens have been described in cells infected in vitro with this virus. Antibodies to these antigens have been detected in the sera of a high percentage of cervical cancer patients. Additionally, soluble membrane antigens extracted from cervical tumors were shown to react with antibody directed against HSV nonvirion antigens. One of these nonvirion antigens, AG-4, appeared in cultured human cells four hours after infection with HSV-2. Antibody to this antigen was found almost exclusively in women with cervical neoplasia, displayed a pattern of increased prevalence in patients with more advanced stages of the disease, and was absent in women who had undergone successful tumor therapy.

Infectious virus, viral structural antigens, and HSV-specific cytoplasmic changes have not been detected in cervical cancer biopsies. However, virion structural antigens were observed in exfoliated tumor cells and tumor cells on the periphery of neoplastic lesions. Further evidence for the persistence of the HSV genome in cervical tumor cells was gathered from in vitro experiments in which infectious virus and viral antigens were detected in spontaneiously degenerating cell cultures derived from a carcinoma in situ. Changes similar to those appearing spontaneously could be induced by exposure of the cells to medium or high pH. Virus expression in a culture derived from an invasive cervical carcinoma was limited to a membrane fluorescence on 2% of the cells which could not be augmented by spontaneous or high pH-induced cell degeneration. This data suggests that some cervical cancer cells harbor the complete HSV-2 genome in a repressed state and virus expression occurs following exposure of the cells to conditions of stress.

Photodynamically-inactivated or UV-irradiated HSV-2 has been shown to transform normal hamster embryo fibroblasts in vitro. A variety of serologic tests have yielded evidence for HSV-specific antigens in the cytoplasm and on the surface of transformed cells. These cells were tumorigenic when inoculated into newborn hamsters and induced virus-neutralizing and membrane reactive antibodies in the sera of tumor-bearing animals. Pre-immunization of hamsters with HSV failed to induce transplantation immunity but instead enhanced tumor metastases while immunization with SV40 inhibited metastases but did not reduce the rate of primary tumor development. Transformation in vitro of hamster cells by UV-irradiated HSV-1 and cytomegalovirus and of human embryonic lung cells by heat-inactivated HSV-2 have also been reported.

These findings strengthen the relationship between HSV-2 and cervical carcinoma, but further studies are needed to determine the exact role of this virus in cervical cancer. If HSV-2 can be shown to play some essential part in the induction of this disease, appropriate control measures may be developed to reduce the incidence of this human cancer.

Papovaviruses. Polyoma virus, SV40 and the papilloma viruses are oncogenic members of the papova group of viruses. The capacity of these agents, particularly polyoma virus and SV40, to produce malignant tumors in several different animals is well known. In addition, SV40 has been shown to transform morphologically a variety of cultured cells, including those of human origin. During the past three years, several papovaviruses of the polyoma-SV40 group have been isolated from humans. These viruses can be classified into three antigenically distinct groups which crossreact to some extent with SV40 but not with polyoma virus. Since seroepidemiologic evidence has been obtained indicating the widespread colonization of human populations by this group of viruses, their role in human neoplasia is being systematically examined.

Treatment and Control

The most impressive evidence for the viral etiology and perhaps the best hope for prevention and control of cancer would be the demonstration that anti-viral agents or anti-viral immune responses can prevent or modify the disease. There are a number of reasons for attempting to use the information now available on RNA tumor viruses in the control of cancer.

(a) The oncogenicity of these viruses in vertebrate species is well-established.

(b) In contrast to chemically-induced tumors, cells transformed by a given virus share common antigens, which are determined by the viral genome, either as virus structural antigens and/or as virus-associated antigens.

(c) Several antigens have been isolated, purified and characterized with respect to the serologic reactivities directed against them. Some of these are expressed at the cell surface whether or not virus particles are produced.

(d) Naturally occurring antibodies to type C virus components and virus-associated antigens have been demonstrated in the animal host. While the correlation of the immune responses with the incidence of malignancy needs to be determined, active or passive immunization may be an approach to the control or prevention of cancers of animals and man.

Immunologic Treatment. Nonspecific stimulation of the host's immune response can be accomplished by a number of chemical agents. Some of the agents that stimulate the reticuloendothelial system nonspecifically, e.g., imidazolethiazole, pyran copolymer, tilorone, BCG, etc., have proven effective in increasing the survival time of leukemic mice. Levamisole has proved especially effective when used in combination therapy and is presently being used in preliminary clinical trials.

Specific stimulation of the host's immune response is achieved by vaccination with viruses, viral antigens or virus-associated antigens. It now appears possible to use virus vaccine-induced antibodies to modify natural type C virus expressions and either delay or prevent tumors associated with these viruses. Early experiments established the feasibility of using formalin-killed virus vaccine in the prevention of murine leukemias induced by infection with the Rauscher strain of MuLV. Since spontaneous virus-induced cancers appear to be caused by endogenous viruses which are present in the animal from the moment of conception, the prevention of malignancy by these viruses is not as straightforward as the prevention of diseases caused by viral infections. However, with some notable exceptions in highly permissive animal systems, most spontaneous cancers in natural species occur late in life. On the other hand, effective virus-specific neutralizing and cell-mediated immune responses to endogenous viruses can be produced early in life by live, attenuated or formalin-killed viral vaccines. Therefore prevention of spontaneous cancers by viral vaccines now appears feasible. Studies to test such vaccines are underway in a number of laboratories but since such studies are of necessity long-term final results are not available at this time.

Any vaccine containing live or inactivated oncogenic viruses has definite disadvantages. There is always the possibility that the viral RNA, alone or in combination with other information in the cell, still has the capacity to transform the cell. In order to avoid this potential hazard, investigators are studying the possibility of using viral antigens free of viral RNA in vaccines. Such antigens can be prepared either by purifying viral proteins or by using preparations of cell membranes that carry viral or virus-associated antigens. Both possibilities are being pursued. The disadvantage to this type of vaccine is that since proteins cannot replicate after injection into an animal as viruses do, a much larger amount of material has to be used to obtain an equivalent immunological response. In man, vaccines of thps type would probably have to be limited to high risk groups.

In this regard, it is interesting that homogenates of tumor cells infected with certain non-oncogenic viruses are more immunogenic than extracts of non-infected cells. For example, extracts of SV40-transformed cells infected with influenza virus or VSV produce much better immunity in mice than do uninfected cell extracts. Viruses which seem suitable for the purpose of "virus-assisted immunotherapy" in man have been adapted to human malignant tissues and a new research strategy towards human application is under way.

Neuraminidase treatment of tumor cells has also been found to increase their effectiveness as immune stimulators. The injection of neuraminidase-treated tumor cells greatly increases the lifespan of AKR mice undergoing chemotherapy. Such cells are now being used in the treatment of patients.

Biochemical Treatment. A number of compounds that specifically inhibit viral functions have been identified. Some compounds, such as colcemid and fluorodeoxyuridine, increase the reversion frequency of certain transformed cells to the normal state. Other compounds can specifically inhibit the viral RNA dependent DNA polymerase. Interferon, an anti-viral agent, has been found effective in reducing cancer incidence in animals receiving grafts. None of the chemicals so far tested promises to provide a magic cure for cancer, but some have proved useful in combination with other treatment.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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