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NEW GUIDELINES DEVELOPED FOR CANCER CONTROL GRANTS TO CENTERS FOR COMMUNITY OUTREACH

A final (until further revisions, at least) draft of guidelines for NCI Div. of Cancer Control & Rehabilitation grant support of cancer centers for community outreach programs is now an operating document for applicants, site visitors and reviewers.

It is mandatory for comprehensive cancer centers to initiate and carry out cancer control programs within their regional areas. DCCR acknowledged that other centers may have outreach capabilities and has agreed that they are eligible for support based upon those capabilities and community needs. Executives of all centers where outreach programs are being planned or contemplated should obtain copies of the guidelines immediately. Write to DCCR, Blair Bldg, 8300 Colesville Rd., Silver Spring, Md. 20910.

The guidelines apply to all three DCCR program areas—single inter-

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In Brief

COMMUNITY PLANNING CONTRACTS NEAR REVIEW, IMPLEMENTATION PROJECTS STILL IN NEGOTIATION

COMMUNITY BASED cancer control contracts, the controversial "saturation" program that weathered severe criticism last year just as the contracts were being awarded, are more or less on schedule. The nine planning contracts will start coming in for review, to determine if they will be carried on to the implementation phase, in July. Some are reported in good shape, some with problems which can be overcome, and one or two, perhaps more, may not make it to implementation. The original implementation awards—to the New Mexico Cancer Research & Treatment Center and the Michigan Cancer Foundation—are still being negotiated. New Mexico's negotiations will be wrapped up in mid-June, with Michigan following sometime before the end of the fiscal year, Sept. 30. . . . CANCER CONTROL contracts with the Clinical Cooperative Groups to expand their clinical research into community hospitals will be awarded soon. NCI received proposals from eight groups, still has three to review. All eight may get contracts. . . . IRWIN KRAKOFF, who heads the Div. of Chemotherapy Research at Memorial Sloan-Kettering, will become director of the Univ. of Vermont Cancer Center. That center is being developed as a prototype cancer center in a rural setting; university officials were delighted to land someone with Krakoff's prestige to run it. . . . WILLIAM HAENSZEL, head of NCI's Biometry Branch in the Field Studies & Statistics Program, has retired from government to accept a position with the Univ. of Illinois. Leonard Chiazze, who FSSP Director Marvin Schneiderman hoped would take over the job, also has decided to leave, returning to Georgetown Univ. Top epidemiologists are hard to find, and Schneiderman isn't the only one going after the few that may be available.

CANCER CONTROL CENTER GRANT GUIDES FOR COMMUNITY OUTREACH DEVELOPED

(Continued from page 1)

ventions, community-based cancer control programs and community outreach. They list these project areas with priority for DCCR funding:

1. Planning and Coordination. In the effort to demonstrate systematic approaches to cancer control activities, the need for planning and coordination is vital. Planning and coordination activities which may be funded by DCCR should include the following characteristics:

a. The analysis of data and information about the demographic and epidemiological patterns in the region to be served, including any unusual disease patterns present in its population.

b. An inventory and analysis of existing cancer management resources, as well as of patient loads and patient flow and referral patterns in the region to be served, including an assessment of resource gaps and cancer control deficiencies.

c. Demonstration of multi-institutional involvement and cooperation, since a major intent of the planning and coordination activity is to reduce fragmentation and duplication of effort.

2. Innovative Interventions. The National Cancer Program has identified five "intervention areas"—prevention, detection, diagnosis and treatment, rehabilitation and continuing care—involved in the management of cancer. DCCR may support activities related to any of the above intervention areas, provided the proposed activities show promise of resulting in new and more efficient or effective approaches to the problem addressed. The intent is not simply to support ongoing activities, but to develop new methods for resolving persistent problems in cancer control.

3. Organized Transfer of Knowledge. A major premise of the Cancer Control Porgram is the need to disseminate the most recent knowledge about cancer management from the research institutions to community physicians and to the hospitals and other medical facilities involved in the care of the cancer patient. DCCR, therefore, places a high priority on the development of professional education programs, particularly if they are done on a collaborative basis with interested agencies and institutions and if they represent an effort to identify and use innovative and possibly more effective approaches to professional education in cancer management.

4. Demonstrations of More Effective Use of Cancer Management Resources. DCCR will fund activities designed to test new approaches to the management of cancer resources in a given region. Demonstration projects will vary widely, but examples of projects that might be considered are the development of multi-institutional approaches to cancer management, such as shared radiotherapy programs; or innovative uses of the team concept in cancer management.

5. Public Information. Since a major factor in the success of cancer control is comprehension and initiative on the part of the public, DCCR will support activities which advance public knowledge about cancer and increase the public's ability to use available cancer management resources effectively. Support will be restricted to demonstrations of new or experimental approaches to public information which promise improved effectiveness either in terms of increased public awareness generally or of increased impact on traditionally difficult-to-reach groups. Cooperation with both government and non-government agencies in developing cancer information programs is strongly encouraged.

In the area of single interventions, both contracts and grants are utilized. Support is provided for investigator initiated or DCCR initiated proposals for specific projects in prevention, detection, diagnosis, pretreatment evaluation, treatment, rehabilitation, continuing care and education. It is the policy of DCCR to continue to support such individual intervention projects through the grant and contract mechanisms.

The second program area listed is that identified as the Community-Based Cancer Control Program. It is directed towards organizing a wide range of community resources, professional and non-professional, financial and social within a limited geographic area and a specific population base. Such community organization efforts will test the hypothesis that the coordinated use of all cancer control interventions in an integrated manner in dealing with certain selected cancers will have a greater impact than a fragmented and/or single intervention approach. It is to be emphasized that this program with a limited time span is very specifically a test to be conducted in a limited number of communities aimed at selected cancer sites. It is not a substitute for, or an alternative to the Cancer Center Outreach Programs. If a Cancer Center falls within the geographic area of a Community-Based Cancer Control Program, the Center's Outreach Program may become an integral and complementary resource to the Community-Ba sed Program. [A report on the status of this program will appear next week in ***The Cancer Letter***.]

The third program area is that of Cancer Center Community Outreach. The term "Community Outreach" has been woven into the Cancer Control Program to label that part of the program under which Cancer Centers can develop a planning and active professional involvement throughout their entire community service areas. It represents a broad planning approach to Community Cancer Control and Rehabilitation through identifying existing control needs and weaknesses, pinpointing professional resources, and fitting necessary program parts into the overall plan. Outreach is primarily oriented to the

needs of the health professional community, and it assumes cooperation of the cancer center with the outlying medical facilities, physicians, and allied health professionals in achieving the most effective detection, diagnosis, treatment and rehabilitation management presently available. Emphasis is directed to helping the community develop its own capability to assume most of the responsibility for the care of patients in its particular area.

Community Outreach Programs involve patterns of need, epidemiologic analysis, regional resource distribution, and establishment of priorities. Also involved are broad professional activities such as education, treatment protocol and design and implementation, physician-network consultation, and cooperative community cancer control projects.

DCCR presently provides support to cancer centers for Community Outreach Programs utilizing both grants and contracts including (1) developmental grants to provide the general administrative and planning support, (2) specific project grants, (3) contracts for information services support.

Developmental and Support Grants

DCCR will provide basic planning, organizational and developmental support to cancer centers having the capability to carry out Cancer Control Programs, the guidelines say. This support is primarily provided by the cancer control developmental and support grant. The scope of the developmental grant includes:

- Define organizational structure for cancer control activities.
- Develop scientific and administrative content of the outreach program.
- Assess commitment of institutions in patient referral areas and private physicians to support cancer control programs and define working relationships among community participants.
- Plan for evaluation of control activities.
- Develop a plan and schedule for implementation of a center-based Community Outreach Program for comprehensive cancer control activities in prevention, early detection, diagnosis, treatment, rehabilitation, continuing care and education.

In developing its community outreach cancer control program, each center will have needs peculiar to its own geographic area and overall program management. Funding support should reflect such differences, and the developmental grant can be flexible in meeting specific needs as they fall within the overall National Cancer Program. Under this developmental and support grant, DCCR funding support can be categorized into (a) personnel, (b) seed funding for start-up project, (c) other allowable support items.

(a) Personnel

An effective cancer control program based within a center requires an organized unit of key personnel under the direction of an associate director for cancer control. This cancer control unit must be provided with the continuing financial stability necessary to plan and implement long-term outreach activities. A center's cancer control program should have sufficient scope to permit the full employment of a developmental staff trained in a variety of disciplines, such as oncology, epidemiology, administration, evaluation and public health, to serve as technical assistance resources to cancer control developmental and program activities in the region. Each center is unique in its staffing needs for its cancer control program. DCCR cancer control developmental and support grants are flexible in providing for these varied personnel. Staffing needs are proposed and justified by each center on the basis of its project program. Staffing should be adequate to provide for such program elements as grant management, cancer control needs assessment, objective setting, project initiation, program evaluation and outreach educational program development.

It is possible that certain personnel utilized in the center's cancer control program might be supported by non-DCCR funding. For administrative reasons, a cancer center might prefer to request support for the associate director for cancer control under its center core grant. Other examples of alternative funding might be biostatisticians and administrators. However, it is the intent of the cancer control developmental and support grant to provide funding for those key personnel engaged in cancer control activities. Such personnel would generally include the associate director for cancer control and the staff serving with him in this capacity. Funding will be provided upon the basis of the percentrage of their time actually spent in cancer control activities. Cancer control personnel funded under the developmental grant should not duplicate personnel in other center departments such as statisticians or epidemiologists who can be utilized and are available for cancer control activities.

Specific types of personnel which may be funded under the cancer control developmental and support grant are listed here only as examples: grants management administrator, assistant director for rehabilitation and primary interventions, health educator, public health specialist, epidemiologist, statistician, and nurse practitioner.

(b) Seed Funding for Start-Up Projects

Under the developmental and support grant, limited funding is available for specific cancer control projects which, if successful, will have demonstration value for the immediate community and for other cancer centers. Such seed funding will be limited to the time frame of the grant. If successful, such project activity should be subsequently continued under funding sources other than DCCR or perhaps by a specific DCCR project grant. In requesting seed funding for cancer control projects under the developmental grant, the requestor should both detail and rationalize the proposed time plan for the project.

It is the policy of DCCR that the developmental and support grant not become the historical "um-

brella grant" under which numerous and varied projects are sheltered from specific peer review and analysis.

(c) Other Allowable Support Items

In addition to staffing support, developmental grant funds can be utilized for:

1. Project-specific equipment.
2. Project-specific supplies.
3. Centralized services applicable to cancer control activities.
4. Travel, with emphasis on travel within the center's service area, for outreach activities.
5. Planning and evaluation.
6. Educational activities.
7. Consultation costs.

As presently determined, developmental grant funds may not be utilized for physician's fees, patient care, hospitalization, construction, or ongoing tumor registry services (except those components specifically related to outreach objectives).

Specific Project Grants

As previously mentioned the single intervention projects in cancer control, investigator initiated or DCCR initiated, are funded by DCCR through grants subject to peer review. Investigators are encouraged to propose projects involving approaches to the innovative demonstration and promotion of control methods. Research in the area of rehabilitation similarly can be funded.

Contracts

A cancer information system is considered an essential component of a cancer center's Community Outreach Program. For this reason, DCCR provides funding support for NCI designated cneters for the development of cancer control information systems for both health professionals and the general public. Through the contract mechanism, it is the intent of DCCR that these communication support contracts be flexible in meeting the specific needs of the individual centers.

In the center's outreach program, heavy emphasis must be placed on the planning component, according to the guidelines. This planning activity will require an adequate staff to develop detailed knowledge of the general population served, patient loads, unusual demographic factors, and characteristics of disease in the region served.

Scientific and administrative content for the outreach program must be developed and the ability to uncover hidden needs and cancer control deficiencies is a must. It is also essential to plan for the evaluation of control activities. It is necessary to develop a plan and schedule for implementation of center-based community outreach program for comprehensive cancer control activities in prevention, early detection, diagnosis, treatment, rehabilitation, continuing care, and education.

It is important that the demonstration aspects of cancer control activities be recognized, and that appropriate time frames be developed for shifting specific project support to alternative funding, the guidelines emphasized.

Grant applications are judged on the basis of peer review utilizing site visits when required. In this review process, answers to the following questions relative to the grant application are considered to be of major importance:

1. What are the specific objectives of the proposed outreach program?
2. Have the objectives been established on the basis of an overall analysis of cancer control deficiencies and needs in the appropriate community area?
3. Do the objectives fit within the DCCR cancer control concept of demonstration and promotion rather than the concept of funding good but well-established health care practices?
4. Have measurable criteria for stated objectives been defined, and has an evaluation plan and timetable been proposed?

The DCCR Grant Review Committee will be asked to assign relative priorities to individual program components of a developmental and support grant application. Such component priorities will be considered whenever subsequent funding cannot provide for 100% support of recommended funding levels.

DCCR pointed out that its Off ice of Community Activities will provide assistance to centers in the development of their outreach programs. Some of the centers have already developed well-defined community programs. DCCR staff assistance can be provided along the entire funding trail from preliminary planning and funding application through final evaluation. It was suggested that centers contact DCCR as early as possible relative to future cancer control grant or contract applications in order that planning assistance and guidance for grant submission might be provided.

DCCR noted that some centers may elect to seek support for certain cancer control activities through the Div. of Cancer Research Resources & Centers core grants rather than through DCCR developmental and support grants.

"This practice should be discouraged," the guidelines said. "DCCR support can only be provided to grant applications which have been assigned to DCCR and reviewed by a DCCR Grant Review Committee. Each center should seek grant support for its cancer control and rehabilitation program activities through either the cancer control developmental and support grant or specific project grants."

NCAB TO HEAR REPORTS ON ENVIRONMENTAL CARCINOGENESIS, INTERNATIONAL RESEARCH

Environmental carcinogenesis and international cancer research activities will share the major portion of the National Cancer Advisory Board's meeting June 21-22.

All but 45 minutes of the two-day meeting will be open. The Board will review grant applications in

closed session June 21, from 11:15 a.m.–noon. The meetings start at 9 a.m. each day.

James Peters, director of the Div. of Cancer Cause & Prevention, will discuss the status of the National Clearinghouse on Environmental Carcinogenesis at 1:30 p.m. June 21. Presentations will follow from Louise Strong, director of the Medical Genetics Clinic at Texas Medical Center, on "Cancer from Interaction of Environment and Genetics in Man;" Gary Flamm, assistant director of DCCP, "Status of In Vitro Test Procedures;" Marvin Schneiderman, director of Field Studies & Statistics, "85% of Cancers Environmentally Induced;" Philippe Shubik, Eppley Institute, "Report of the NCAB Subcommittee on Environmental Carcinogenesis;" and Robert Huebner, chief of the Laboratory of RNA Tumor Viruses, "Why Not Prevention?"

International activities reports form the morning agenda for June 22. Gregory O'Conor, NCI associate director for international affairs, will lead the discussion. John Higginson, director of the International Assn. for Cancer Research in Lyon, will report on that organization's international surveillance program proposal. Henry Tagnon, president of the European Organization for Research on Treatment of Cancer in Brussels, will discuss his organization's activities. Thomas Connors, head of the Dept. of Biochemistry at the Beatty Research Institute in London, will report on chemotherapy model systems and drug development. And Noel, Warner, of the Walter & Eliza Hall Institute of Medical Research in Victoria, Australia, will present an overview of cancer immunology.

Peter Mozden, Boston Univ., will talk on clinical education to open the June 22 afternoon session. Frank Dixon, chairman of the NCAB Subcommittee on Planning, will review cancer program five year projections, from 1978-1982, and the 1978 budget, assisted by NCI executives Louis Carrese, Calvin Baldwin and Earl Browning.

BIOMEDICAL PANEL REPORT SAYS CANCER PANEL SHOULD EXPAND TO SERVE ALL NIH

The report of the President's Biomedical Research Panel, which some cancer program advocates feared would be used to bludgeon the cancer effort, professes strong support for the National Cancer Program and the special authorities granted by Congress to NCI. But a major recommendation of the report, if carried out, could result in watering down those authorities and pushing NCI back to where it was in 1971 in the NIH-HEW hierarchy.

That recommendation calls for expanding the role and membership of the President's Cancer Panel and giving it responsibility for all NIH research. The result inevitably would lead to just the situation Congress hoped to avoid in creating the Panel–it was intended to serve as an advisory group with direct access to the President and with no conflicting loyalties to any health effort not related to cancer.

The Cancer Panel has done its job well. Attempts by former Asst. Secretary for Health Charles Edwards, former HEW Secretary Caspar Weinberger, and by the Office of Management & Budget to raid NCI funds for other programs, kill training programs, limit staff positions to unrealistically low levels, deny cancer center construction funds, and to deliberately misinterpret provisions of the Cancer Act to impede the program all have been opposed with considerable success by the Cancer Panel.

The Biomedical Panel Acknowledged this. "We recognize that the Cancer Panel has been a valuable asset to the National Cancer Program, although it is unorthodox." But the report suggested that an expanded Panel could serve other NIH efforts while remaining an effective force for the Cancer Program. The report states:

"In order not to have two NIH panels with separate memberships, and in order not to interfere at this time with the procedures of the National Cancer Program as established by Congress, we recommend that the President's Cancer Panel also be constituted by statute as the President's Biomedical Research Panel, retain its present responsibilities with regard to the National Cancer Program, and exercise similar responsibility for the programs of NIH. These functions require the appointment of members to the Panel who are well qualified to deal with both the broad functions of NIH and the more specific problems of the National Cancer Program. The proposed Panel should effectively serve both the NIH biomedical programs and the National Cancer Program, not only without conflict but with enhanced coordination of the complimentary activities. This proposal provides the opportunity, if experience so dictates, to fully integrate the National Cancer Program with the programs of NIH in due time."

Congress very nearly took NCI completely out of NIH in 1971, when the Cancer Act was being developed, explicitly so that NIH could not "fully integrate" the Cancer Program with other NIH programs and thus permit the spreading of cancer funds around to suit the whims of the various secretaries and assistant secretaries. Congress is not likely to accept the report's advice.

The report noted that Benno Schmidt, chairman of the Cancer Panel and a member of the Biomedical Panel (which was scheduled to go out of business upon submission of the report) "did not participate in the final decision that led to this recommendation because he currently serves as chairman of the President's Cancer Panel. He concurs in the view that it is preferable not to have two panels with separate membership and that it is possible to find appointees well qualified to serve in this dual role. If this recommendation is implemented, Mr. Schmidt would favor the President's making new appointments to the President's Cancer Panel in order to give the President full latitutde in designating persons best qualified for this

new dual responsibility."

The Panel suggested that the NIH director should play a greater role in the Cancer Program, again contending that this would not reduce NCI's independent authority.

"The Panel believes that the Director, NIH, should be the central figure at NIH accountable for planning and decisionmaking. It does not recommend that the special status of the NCI be changed at this time. Rather, to support a central role for the Director, NIH, we have recommended, in the previous section, that the current President's Cancer Panel be expanded to provide the same overview function to all of the NIH that it now provides for the National Cancer Program. While the Director, NCI, will still retain a special budget bypass authority, full opportunity should be given to the Director, NIH, and the NIH Advisory Board to consider the implications of budget and legislative requests of NCI in a timely fashion before submission of such requests to the President and Congress."

The report discussed the special status of NCI and supported its continuation, finding that the Cancer Program had—contrary to fears expressed in 1971—actually strengthened NIH, rather than contributing to its breakup.

"The passage of the National Cancer Act of 1971 gave new authority to NCI. The Panel heard testimony indicating that some members of NIH and the larger scientific community felt that the special status of NCI created an imbalance in the national biomedical research effort. Further, the Panel heard allegations that within NCI the administration of the program was uneven in the matter of quality control and in allocation of resources to the several segments of the program. Beyond this, at the inception of the National Cancer Program, there were some who perceived the special status of NCI as the first step in the breakup of the NIH. Time has not proved this to be the case. NCI remains a part of the NIH, and, indeed, has strengthened the general research effort of the NIH.

"Further, after examining this matter in as much depth as possible, the Panel concludes that on balance the National Cancer Program continues to serve the nation's interest well. We especially applaud the commitment of NCI to fundamental research, which, in the end, will benefit the attack on a variety of diverse disease categories, as well as on cancer itself.

"The Panel both recognizes and supports the priority for cancer research established by Congress. In the total range of its recommendations, however, the Panel is seeking to strengthen the character and operation of *all* the Institutes of the NIH with a view of assuring that, in the future, high-priority biomedical research and related action programs can be pressed effectively by NIH within its own management structure without the need for the Congress to provide special arrangements."

The report did not really address itself to the question of information dissemination and application—the issue of whether or not NIH should be involved in control programs. The issue has developed since the advent of the Cancer Control Program, and some had expected the Panel to take a strong position one way or another.

Instead, the report cited the differing opinions:

"The congressional authorizations in 1971 and 1972 for high-priority programs in cancer and heart disease greatly expanded the scope of NIH in knowledge application and dissemination and moved it closer to conducting clinical service programs. Many in the science community prefer that NIH revert to a "pure" research institution. Others feel that this new responsibility is appropriate and that the mission of NIH encompasses knowledge applications in the interest of improving health care and public well-being.

"Congress has provided special funding for selected elements of knowledge application and dissemination in several of the institutes, but at the same time, other institutes were denied adequate resources to meet even their basic research missions."

The report claims that NIH is on the verge of health care delivery and says that both health service and health service research belong in other agencies.

The report calls for the appointment of a science advisor to the President and says that OMB " should not make science decisions as it has in the past without strong scientific guidance." The science advisor and a strong director of NIH "should provide OMB with access to excellent scientific advice."

ABSTRACTS OF OUTSTANDING PAPERS PRESENTED AT ANNUAL AACR MEETING

The program committee for the 67th annual meeting of the American Assn. for Cancer Research selected 44 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list, chosen from sessions on clinical pharmacology, biochemistry, chemical carcinogenesis, immunology, virology, and clinical investigations. Others appeared in the previous two issues of ***The Cancer Letter*** and additional abstracts will be published in subsequent issues.

ANTIGENS OF HUMAN ACUTE MYELOMONOCYTIC LEUKEMIA (AMML) AND CHRONIC GRANULOCYTIC LEUKEMIA CELLS IN BLAST CRISIS (CML-BC): SEROLOGIC STUDIES WITH SIMIAN ANTISERA – T. Mohanakumar, Donald Miller and Richard Metzgar, Duke Univ.

Nonhuman primate antisera to different morphological classes of human leukemia cells after absorptions with normal buffy coat leukocytes are cytotoxic to leukemic cells. These antisera are capable of differentiating between antigens associated with lymphocytic and myeloid leukemias (J.N.C.I. 52:1435, 1974).

In this study, cells from AMML and CML-BC patients were tested with our panel of cytotoxic simian antisera. Antisera to both lymphocytic and myelogenous leukemia cells lysed peripheral blood or bone marrow cells from all relapse or untreated AMML patients and most of the CML-

BC patients. In contrast, cells from acute meylogenous leukemia and CML donors not in blast crisis are lysed only by the antisera to myelogenous leukemia antigens. Cells from AMML and CML-BC patients were also lysed by a non-human primate antisera detecting normal human peripheral blood thymus derived lymphocytes (T-lymphocytes). The percentage of cells lysed by the various antisera and absorption experiments suggest that some cells from AMML and CML-BC patients express membrane antigens associated with both lymphocytic and myelogenous leukemias as well as T-lymphocyte antigens.

Serologic analysis with simian antisera may be a new approach to nosology of leukemia and provide some insight into the origin and nature of the leukemia cell.

THE RELATION OF HEPATITIS B INFECTION TO PRIMARY HEPATIC CARCINOMA AND CHRONIC LIVER DISEASE IN WEST AFRICA – Bernard Larouzé, W. Thomas London, Gerard Saimot, Maurice Payet, Baruch Blumberg, The Institute for Cancer Research, Fox Chase Cancer Center, and Institut Leon M'ba, Hospital Claude Bernard, Paris

We are testing the hypothesis that primary hepatic carcinoma (PHC) is the result of a sequence of events beginning with infection with hepatitis B virus (HBV)→hepatitis→chronic liver disease (CLD)→PHC. Sixty patients with PHC and 42 with CLD from Mali and Senegal, and age, sex, and ethnic group matched controls were tested for hepatitis B surface antigen (HB_SAg), antibody to HB_SAg (anti-HB_S), antibody to hepatitis B core antigen (anti-HB_C), and alphafetoprotein (AFP). HB_SAg was detected in 83% (Senegal) and 47.6% (Mali) of PHC patients compared with 27% and 5.2% in controls. 90% (Senegal) and 75% (Mali) of PHC patients had anti-HB_C compared with 27.6% and 25% in respective controls. Anti-HB_S was more common in controls (45-55%) than in PHC patients (21-38%).

46% of CLD patients (Mali) were HB_SAg(+) and 59% anti-HB_C(+) whereas 5% of controls were HB_SAg(+) and 16% anti-HB_C(+). Anti-HB_S was similar in patients and controls (approx. 30%). AFP was elevated in 7/40 CLD patients and 4/142 controls. 6/7 AFP(+) CLD patients were HB_SAg(+).

These data are consistent with the hypothesis and suggest that prevention of infection with HBV with a vaccine may also prevent PHC.

VIROGENE AND ONCOGENE EXPRESSION IN AKR MOUSE CELLS – E.F. Hays, D.L Vredevoe, M.A. Nicolson, R.M. McAllister, UCLA and Children's Hospital of Los Angeles

Virogene expression as measured by XC plaque forming virus and oncogene expression as measured by in vivo oncogenicity were evaluated in neoplastic and normal tissues from AKR mice. XC plaques were measured by the method of Rowe, et al. (Virology 42:1136, 1970) on NIH 3T3 cells. Oncogenicity was measured by lymphoma development within 180 days after inoculation of test material into newborn AKR mice. (1) Filtrates of lymphoma cells from mice with lymphoma accelerated by neonatal inoculation of Gross virus were strongly positive for virogene and oncogene expression. (2) Filtrates from this lymphoma passaged by cells in 2-month-old mice expressed only virogene. (3) Supernatants of an in vitro cell line from a virus accelerated lymphoma were oncogenic but did not express virogene. (4) NIH 3T3 cells infected with filtrates from 2-month-old normal AKR tissues yielded supernatants which were plaque forming but not oncogenic. Host range studies of filtrates (1) and (2), measuring reverse transcriptase and P30 antigen, showed only N-tropic virus.

These studies show that oncogene expression is repressed in young animals as well as when lymphoma cells are transplanted in young immunocompetent hosts, and that lymphoma cells can replicate in vitro without expression of virogene.

INDUCTION OF ONCORNAVIRUS ANTIGENS BY HERPES SIMPLEX VIRUS – Cathy Reed and Fred Rapp, Pennsylvania State Univ.

We have investigated the interaction of endogenous C-type viruses with superinfecting herpes simplex virus type 2 (HSV-2) in mouse cells. Initial experiments with outbred Swiss 3T3 cells yielded less than 2% cells positive in indirect immunofluorescence tests using rabbit serum against murine gs-3 antigen. When these cells were infected with HSV-2 strain 333, 5-10% of the cells became positive for HSV-associated and gs-3 antigens within 3 hours post-infection (p.i.) At 9 hours p.i., the antigen-positive cells had increased to 20%. Normal rabbit serum did not react with the infected cells. We have also examined a line of NIH Swiss mouse cells that are non-inducible for oncornavirus antigens by conventional methods. These cells were induced to express gs antigens following HSV-2 infection. At 10 hours p.i., 100% of the cells were positive for both gs-3 and HSV-associated antigens. Normal rabbit serum did not react with infected cells and uninfected cells were negative with the immune sera.

These findings suggest that infection with HSV-2 induces expression of the gs-3 antigen of endogenous virus present in mouse cells.

PHENOTYPIC ALTERATIONS OF INHERENTLY SUSCEPTIBLE HUMAN SKIN FIBROBLASTS TRANSFORMED BY KIRSTEN MURINE SARCOMA VIRUS – Lawrence Pfeffer, Levy Kopelovich and Martin Lipkin, Memorial Sloan-Kettering Cancer Center

A predisposition to develop neoplasia is associated with hereditary adenomatosis of the colon and rectum (ACR). In this study, the phenotypic alterations of skin fibroblasts (SF) derived from normal-appearing skin biopsies of ACR individuals prior to and following transformation by Kirsten Murine Sarcoma Virus (KiMSV) were investigated. SF cultures were plated in complete EMEM with fetal calf serum (FCS) at a density of $4x10^3$ cells/cm^2 and counted daily for five days. Viral transformation of SF was carried out on day 1 post-plating in the presence of DEAE-dextran for 1 hr, followed by a 2 hr incubation with rat-adapted KiMSV at a titer of $5x10^5$ FFU/ml on rat NRK cells. Focal areas of highly refractile cells were scored 14 days post-infection. Mock-infected cultures from ACR subjects grew in 1% FCS, but did not grow in methocel, nor did they form tumors in athymic mice. Following transformation by KiMSV, these SF showed loss of anchorage dependence and formed tumors in athymic mice. SF taken from non-ACR individuals were contact-inhibited, did not grow in 1% FCS and were 100-1000 fold less susceptible to transformation by KiMSV than SF derived from ACR subjects. The results suggest that SF derived from ACR individuals are phenotypically preneoplastic with increased sensitivity to viral transformation.

TRANSFER OF TUMOR IMMUNITY IN VIVO USING CYTOTOXIC CELLS GENERATED IN VITRO IN A SECONDARY IMMUNE RESPONSE TO SYNGENEIC RAT LYMPHOMA CELLS – Irwin Bernstein and Peter Wright, Fred Hutchinson Cancer Research Center

Cells generated in a secondary immune response in vitro to a syngeneic W/Fu Gross virus induced lymphoma (C58NT)D were tested for their ability to lyse (C58NT)D cells in vitro and inhibit tumor growth in vivo. Spleen cells obtained from rats 4-6 weeks following immunization with (C58NT)D cells (immune cells) lack cytotoxic activity against ^{51}Cr labelled (C58NT)D cells in vitro. However, following in vitro cultivation with mitomycin C-treated (C58NT)D cells (but not with thymocytes), they generate specific cytotoxic activity for (C58NT)D target cells. Optimal generation of cytotoxic cells occurred 5 days following initiation of culture with a 30:1 responding:stimulating cell ratio. 10^7 or $3x10^6$ immune spleen cells sensitized in vitro with (C58NT)D cells inhibited tumor growth in vivo when inoculated as a mixture with 10^6 (C58NT)D cells (Winn test); corresponding numbers of immune spleen cells incubated with syngeneic thymocytes did not. Systemic transfer of immunity was shown when $25\text{-}75x10^6$ in vitro sensitized cells inoculated via the intracardiac route into non-immune recipients resulted in delayed hypersensitivity reactions and inhibition of tumor growth at the intradermal inoculation site of 10^6 (C58NT)D cells.

The results show that immune cells cultured with tumor become cytotoxic in vitro and suppress tumor growth in vivo.

STRUCTURE OF GUANOSINE CONJUGATES FORMED BY REACTION OF POLY(G) WITH 7,12-DIMETHYLBENZ[a] ANTHRACENE-5,6-OXIDE (DMBA-OXIDE) – A.M. Jeffrey, S. Blobstein, I.B. Weinstein, H. Kasai, I. Miura, K. Nakanishi, and R.G. Harvey, Columbia Univ. and Univ. of Chicago

The reaction of arene oxides with nucleic acids has been studied by a number of groups. However the structures of these adducts, which is essential knowledge for a full understanding of the carcinogenicity of polycyclic aromatic hydrocarbons has not been previously elucidated. In earlier studies we showed that covalent binding of DMBA-oxide to RNA occurs primarily on the guanine base and that identical derivatives are formed by reaction with poly(G). Utilizing high pressure liquid chromatography we have now purified four major products from hydrolysates of poly(G) previously reacted with DMBA-oxide. Comparison of uv, mass, and nmr spectra obtained from these derivatives, at both the nucleoside and base levels and before and after acylation, indicates that all four compounds result from substitution on the N-2 amino group of guanine. Two derivatives are substituted at the 5 and two at the 6 position of DMBA to give 5,6-dihydromonohydroxy DMBA derivatives.

The problems associated with the distinction between cis and trans additions will be discussed. Similar techniques are currently being applied to the analysis of various polycyclic aromatic hydrocarbon-nucleoside conjugates formed in vivo and in vitro.

ABSENCE OF RIBOSOMAL NUCLEASES IN NEOPLASTIC TISSUES – Peter Pulkrabek, Raymond E. Jones and Dezider Grunberger, Columbia Univ.

This study was undertaken to delineate differences in the process of regulation of protein synthesis between normal and tumor cells. We have compared polysomes from normal rat liver, bone marrow and mammary gland with that of MOrris hepatoma 7777, chloroleukemia and mammary tumor DBAH. After incubation at 37° polysomes from normal tissues unlike those from tumors are degraded and are much less active in protein symthesis in vitro. These differences are caused by nucleases which are firmly bound to ribosomes of normal tissues. The nucleases could be removed from ribosomes by 1 M KC1 extraction; they split RNA at pyrimidine residues and could be inhibited by liver cytoplasmic RNase in neoplastic ribosomes.

The absence of nuclease activity in ribosomes from neoplastic tissues suggest that different mechanisms of regulation of protein synthesis are involved in normal and tumor tissues.

METHOTREXATE-CITROVORUM (MTX-CF): EFFECT OF ALKALINIZATION (ALK) ON NEPHROTOXICITY AND OF WEEKLY SCHEDULE ON RESPONSE – Susan Pitman, D. Landwehr, N. Jaffe, E. Frei III, Sidney Farber Cancer Center

The major limitation to high dose MTX-CF is crystalization nephrotoxicity, with resultant prolonged MTX plasma T½ (8-20 hours as compared to a normal 4-6 hours), inadequate rescue and marrow and gut toxicity. MTX nephrotoxicity has been demonstrated by the presence of MTX tubular casts and by prompt (within 24 hours) elevation of serum creatinine (SCr. Since MTX solubility is 10-fold greater at pH 7 than at pH 5.4, $NaHCO_3$ was given p.o. to maintain the urine pH >7. All patients had normal IVP's and pretreatment creatinine clearances >60 ml/min. Fifteen patients received 127 weekly courses with ALK. The results were compared to the 33 non-ALK patients receiving 73 courses given tri-weekly. The ages and MTX doses (1-7.5 g/m^2) were comparable. A significant (>50%) elevation of SCr occurred in 29% of the non-ALK courses and in 4% of the ALK courses (p=.02). Myelosuppression occurred only in patients developing nephrotoxicity (20% of the non-ALK and 1.6% of the ALK courses). In 4 patients with elevated SCr at 24 hours, an increase in CF dose rate prevented biochemical and hematologic evidence of myelosuppression. In patients with measurable osteogenic sarcoma, objective responses occurred in 9/13 patients with weekly MTX-CF and in 5/14 patients with tri-weekly (p=> .05)

Thus, weekly MTX-CF can be given safely and may provide improved antitumor effect.

SOLE SOURCE NEGOTIATIONS

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

Title: Isolation of infectious type C viruses from cultured human leukemic cells
Contractor: Sidney Farber Cancer Center.

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 ECI-SHP-75-111

Title: *Inhalation bioassay of cigarette smoke in pigeons*
Deadline: *Aug. 23*

Effects of nicotine and carbon monoxide on atherogenesis will be studied. Award will be dependent on the availability of funds to support this project.

Enviro Control Inc.
One Central Plaza
11300 Rockville Pike
Rockville, Md. 20852
Attn: Subcontracts Administrator

CONTRACT AWARDS

Title: Optimizing electrophoretic separation of proteins with new hydogels
Contractor: Polysciences Inc., Warrington, Pa., $79,611.

Title: Organization and dynamics of cell surface membrane components
Contractor: Tufts-New England Medical Center, $89,073.

Title: Detection of antigen-binding activity of transplantable T-cell tumors
Contractor: Health Research Inc., Buffalo, $37,054.

Title: Nature and function of immune-related cells in tumor masses
Contractor: Scripps Clinic & Research Foundation, $98,000.

Title: Organization and dynamics of cell surface membrane components relevant to tumor immunology
Contractor: Univ. of Washington, $29,981.

Title: Selective stimulation or suppression of immunologic responses
Contractor: Wellcome Research Laboratories, Beckenham, Kent, England, $16,590.

Title: Serologic and immunogenetic investigations
Contractor: Melbourne Univ., Victoria, Australia, $50,456.

Title: Incorporation of five additional alteration/renovation projects as necessary for the performance of the cancer research program being conducted at the Frederick Cancer Research Center
Contractor: Litton Bionetics, $89,026.

The Cancer Letter—*Editor* JERRY D. BOYD

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