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RESEARCH EDUCATION CONTROL

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CHANGES IN COOPERATIVE GROUPS AS RESULT OF MOVE TO DCT TOPIC OF CHAIRMEN'S MEETING SEPT. 16

The nature, extent and timing of possible changes in the Cooperative Clinical Trials Program as the result of the program being moved into NCI's Div. of Cancer Treatment will be the primary topic of a meeting of cooperative group chairmen Sept. 16 in Bethesda.

NCI Director Frank Rauscher said in a memo to group members announcing the switch that he was committing himself "to increased funding and staff support for the groups to the fullest extent possible in order to insure that they become multi-modality oriented, continue to develop a strong statistical base, and pursue new leads in cancer treatment as quickly as is scientifically sound."

The move away from emphasis on drug testing to a multidisciplinary approach, combined with the determination of Rauscher and DCT Director Vincent DeVita to coordinate work of the cooperative groups with other clinical programs will bring about such changes as:

* Phasing out some groups or combining them with others.
* Expansion of some groups to include additional disciplines.
* Development of new protocols to effect the multidisciplinary, multimodality approach and to help achieve the desired coordination with DCT contract supported clinical trials.

(Continued to page 2)

In Brief

ACCC MEETING MOVED TO JAN. 31 IN JACKSONVILLE; ACS GYNECOLOGIC CANCER MEETING SEPT. 18-20 IN PHILA.

SEPTEMBER MEMBERSHIP meeting of the Assn. of Community Cancer Centers, scheduled for Chicago, has been postponed to Jan. 31-Feb. 1, switched to Jacksonville, Fla. Workshop topics will be: Sources of funding for planning, organizing and implementing community cancer programs; elements required for development of a community cancer program; and development and utilization of paramedical personnel in the practice of oncology. For registration information, write to Jacksonville Meeting, ACCC, PO Box 30279, Bethesda, Md. 20014. . . . **NATIONAL CONFERENCE** on Gynecologic Cancer, sponsored by the American Cancer Society, is scheduled for Sept. 18-20 at the Marriott Hotel in Philadelphia. Topics include: New concepts in gynecologic oncology, advances in diagnostic techniques, research in gynecologic oncology, advances in therapeutic techniques, and current status of the treatment of the sites of gynecologic cancer. Write to S.L. Arje, M.D., ACS, 219 E. 42nd St., NYC 10017. . . . "**THERE'S NO** holdup of good therapy by the failure of FDA to move aggressively (in approving new drugs for research)?" asked President's Cancer Panel Chairman Benno Schmidt. Vincent DeVita, director of NCI's Div. of Cancer Treatment, said there is not. NCI has investigational new drug applications on about 50 drugs in various stages of research development.

MAJOR PROBLEM IN CLINICAL RESEARCH —COMPETITION FOR CANCER PATIENTS

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* Supplementing the grant funds of certain groups with DCT contracts.

The group chairmen may also hear at the Sept. 16 meeting about various procedural changes brought about by the switch. DeVita probably will call more meetings of the group chairmen, who have rarely been convened in the past. The Cancer Clinical Investigation Review Committee, which oversees the program, is now an advisory group to DCT rather than the Div. of Research Resources & Centers.

DRR&C will continue to administer cooperative group grants and process applications.

Rauscher's decision to move the cooperative groups into DCT climaxed the struggle involving NCI staff members and their various constituents around the country. The need to coordinate the many and growing treatment research programs was obvious. DCT could fund its extramural efforts only through contracts, while clinical research grants were awarded and administered by DRR&C. Complicating the problem was the fact that a major treatment program was carried on by the Div. of Cancer Biology & Diagnosis. NCI's clinical director, who conducts the intramural clinical research program, was located in DCB&D.

Earlier this year, Rauscher moved the clinical director and the radiation and surgery branches from DCB&D to DCT. But the cooperative groups were the major problem as far as coordination was concerned, Rauscher and DeVita agreed.

DeVita reviewed the situation last week for the President's Cancer Panel, covering efforts of DCT to work with the groups. In a report prepared by DeVita and his deputy, Stephen Carter, he noted that DCT holds the INDs for all the investigational drugs utilized by the groups, and supplies all drugs used by the groups in their studies. Carter or other DCT staff members attend group meetings and circulate memos summarizing them; Carter cosigns letters to group chairmen informing them their protocols have been filed; DCT sponsors new drug liaison meetings to which group chairmen were invited; and Carter is an official member of CCIRC.

Yet, "while this achieved communication it achieved little coordination and in no way prevented unwanted duplication, lack of coordination between group studies and the contract-supported studies, or the competition for and fragmentation of clinical resources," the DeVita-Carter report said. "Also, no central planning function has ever been identified for both groups and contracts."

The report concluded that "reasonably good communication exists but this is primarily informational. Planning to assure coverage of gap areas and avoidance of unnecessary overlap, competition for resources, or use of resources is minimal."

Panel Chairman Benno Schmidt couldn't resist putting some pressure on DeVita. "You're in the driver's seat now, aren't you, as far as coordinating with the cooperative groups is concerned?"

DeVita agreed that he was, and mentioned the meeting with group chairmen as the place coordinating would begin.

The DeVita-Carter report touched on coordination with other clinically-related programs. Coordination with organ site task forces has been conducted through joint membership on task force therapy committees and DCT organ site working groups. A formal liaison between DCT staff and Cancer Control has recently been established to facilitate flow of information of all potential new projects to Control. But no formal mechanism now exists for transmission of information from traditional grant supported studies on treatment to other areas. This is generally achieved by word of mouth or presentation at scientific meetings.

Schmidt commented, "You don't want a mechanism where a grant needs approval of DCT. It would be very easy to say to an applicant, 'Oh, hell, we're already doing that.' If a grantee turns up something, it will get known."

Thomas King, DRR&C director, said that an informal mechanism exists in the form of a summary statement after the award is made.

The DeVita-Carter report emphasized what is probably the major problem facing clinical research programs—the shortage of cancer patients.

"We know the important questions, and have the necessary tools to perform the required experiments," the report said. "What we don't have is the proper patient population—the patient with early cancer, who although the tumor is removed, has a high risk of recurrence and subsequent death from cancer. . .

"We have three major treatment resources of patients with cancer in this country, cancer centers, the clinical cooperative groups and those patients in the private community. . . . Twenty one thousand patients enter group studies each year but 85% are still patients with advanced cancer. About 5,000 patients are treated under contract with DCT and 55% have localized disease. . . . The major patient resources needed for the therapeutic experiments of the next decade are largely in the private community, largely seen first by surgeons. It is notable that surgeons are uncommon members and even more uncommon chairmen of any of the existing cooperative groups. The most glaring and most effective exception is that of Dr. Bernard Fisher, who chairs the National Surgical Adjuvant Breast Project, which is a unique, flexible and model group in its own right.

"The institutions most likely to gain the confidence of the private community and access to the patient material is that institution with a multidisciplinary base. This description most fits the emerging cancer centers, whether they are within or outside

the cooperative group mechanism and their closer integration into the operation of the cooperative groups is important. . . .

"The way seems clear. New therapies tested in patients with advanced cancer should be applied to those with localized disease who have a high risk of recurrences. Positive results have already been achieved using this approach. Improved survival will undoubtedly follow. . . .

"What is needed most of all is planning to avoid missing opportunities for application of the results of basic therapeutic research as has happened all too frequently in the past (e.g. breast cancer, what is being done today was quite possible to do 15 years ago). Planning is necessary if we are to assemble the ingredients of the experiment all in the same vicinity, the patients with early disease, recently diagnosed, and the small but growing supply of sophisticated therapeutic cancer investigators.

"Investigator initiated therapeutic research obviously should not be stifled in any way but encouraged, but we have tended to misinterpret where it comes from. The contract mechanism can be used to supplement the grant supported cooperative groups and is a rapid method of developing leads in therapeutic research."

The report summarized DCT's extramural clinical trials conducted by contract. This program has two major thrusts—clinical evaluation of new anticancer drugs, and development of optimal therapy for specific tumor types by using combined modality approaches.

"Increased emphasis on the integration of chemotherapy into a series of disease oriented strategies leads to a conflict between the clinical resources needed by the Drug Development Program and the exigencies of devising an optimal combined modality treatment strategy for solid tumors," the report said. "This conflict is most critical in allocating clinical resources in the advanced disease states of different tumors. . . .

"The need to rapidly test new agents in several tumors to determine their potential in the therapeutic armamentarium leads to the Phase II-III trials by contract. Many such studies are also conducted by cooperative groups, and it is here that the overlap of studies is significant. The use of this mechanism (the contract) in the search for patients not previously available in the cooperative groups has been successful since we estimate that about 55% of the approximately $10 million in clinical contracts is devoted to studies in patients with regional or local tumors."

SCHMIDT'S DOUBTS THREATEN SATURATION PROGRAM; NCAB TO HEAR REVIEW IN OCT.

NCI's ambitious "community saturation program," an experiment by the Div. of Cancer Control & Rehabilitation to marshal all the forces within a geographic area to develop optimal cancer care, is in jeopardy.

Benno Schmidt, chairman of the President's Cancer Panel, has expressed misgivings about the program's practicality and ultimate value. As the result, NCI will hold up award of implementation contracts, to Detroit and New Mexico, until after the program is explained to the Panel and National Cancer Advisory Board in October. The delay will not affect the nine planning awards already made, but a decision to modify or abandon the program would of course affect those awards also.

NCAB's next meeting is Oct. 6-8, with the saturation program discussion scheduled for the final day.

Schmidt said he knows of "no single instance that has attracted as much attention" as the saturation program. He indicated he has heard some rather strong reaction from some of the community organizations which tried but failed to get planning or implementation contracts.

Schmidt commented that the broad objective of the Cancer Control program—to bring the best possible cancer treatment within reach of all cancer patients— involves the total health care delivery system in the United States. "But we can't have those optimal results with the expenditure of the few million dollars available to Control. Yet anything that has to do with getting better care to people is a proper application of cancer control funds. That's Diane's (Fink, DCC&R director) dilemma, and our dilemma."

As for the saturation program, "As I understand its philosophy," Schmidt said, "we take a definite geographic area, reasonably arrived at, and in this case it is Detroit and New Mexico, and try to see what would happen differently than what happens today if everything possible is done to see that everyone in the area gets the best cancer care possible, and we will measure the result. What bothers me is that the objective is unattainable. There is no way NCI can see that everyone in Detroit gets the best possible care. . . . If it were, the next question is, how much will it cost? And is this the best use of our money? And why New Mexico and Detroit?"

Another question, Schmidt said, was whether the RFP or grant application are feasible devices in dealing with a community involving a number of organizations.

One of the key elements of the saturation RFPs was the requirement that various organizations which could play roles in enhancing cancer care join in a collaborative program, with one of them as the "lead" agency to pull it all together.

"How much does a community turn off on a self-appointed organizer who is ordained, or not ordained, by us?" Schmidt asked. "Then he doesn't get the contract, and has to go back and say, 'I'm sorry.' Next time someone wants to organize that community, he's out of luck. The comprehensive cancer centers we have in New York City can't organize New York. They can work with the others, but the minute

one asserts a role of primacy, all you get are arguments rather than cooperation.

"To make a condition of him getting the contract that he's already pulled people together, then tell him he didn't get the contract anyway, is something new for NCI."

Panel member Lee Clark asked, "Don't you think some will go ahead and try on their own, to show they can do it without us?"

Fink said she has learned that some of the unsuccessful proposers are planning to go ahead with the program in their communities with private funds.

NCAB Chairman Jonathan Rhoads commented that "The communities which are the worst organized need the money the most, and those best organized need it least."

The saturation program was developed as a demonstration effort, to determine the extent of improvement possible with an all-out effort. NCI support would end in five years. Theoretically, a significant improvement in survival rates would encourage other communities to undertake similar efforts financed with private, local or state funds.

NEW CANCER CONTROL GRANT GUIDELINES INCLUDE COMMUNITY RESOURCES WORK

New guidelines for the Div. of Cancer Control & Rehabilitation grant programs have been announced covering the division's three major intervention areas and a special category for community resource development.

The grants program is intended, NCI said, to allow the initiation of new concepts in a more effective utilization of existing procedures and/or techniques; and to provide information on the refinement of established procedures and/or techniques for a more vigorous prosecution of cancer control.

Grants may be utilized as a mechanism for support in the following areas:

Prevention

1. The application of identified methods and techniques to inform and stimulate health professionals and the public to fully utilize available cancer prevention services. Such projects are to be oriented toward avoiding the occurrence of the disease through prevention efforts, especially methods and techniques for reducing the exposure to carcinogens, and must include the testing and evaluation of all preventive activities proposed.

2. Programs for the development of cessation strategies involved with cigarette smoking and alcohol consumption.

3. Programs for understanding the determinants of consummatory behavior as they relate to cancer prevention strategy.

Detection, Diagnosis, and Pre-Treatment Evaluation

1. The assessment and evaluation of screening/detection systems with special emphasis on determining the appropriate interval of screening procedures and the cost-effectiveness of various screening-detection systems.

2. Studies designed to develop a better understanding of the factors which motivate and/or inhibit primary health care personnel and the public from dealing more appropriately with early detection, diagnosis, and pre-treatment evaluation.

3. Innovative studies designed to improve the techniques and procedures for effective utilization in appropriate settings of professional assistants in the detection/diagnosis of cancer.

4. Studies to re-evaluate presently accepted or evaluate newer methods for pre-treatment evaluation and to promote the development of criteria and standards for pre-treatment evaluation directed toward defining adequate, acceptable, and structured approaches to pre-treatment evaluation of the patient as required to choose the most appropriate treatment regimen.

Rehabilitation/Continuing Care

1. Research on the management of pain in cancer patients.

2. Research studies on the psychological and psychosocial aspects of cancer as it affects the patient, the patient's family and health professionals. This area may include:

a. The development of new procedures and techniques for counseling cancer patients, their families, and the health personnel dealing with cancer patients.

b. Studies of attitudes and behavior as they relate to the delivery of rehabilitation and continuing care.

3. Research studies on the dietary and nutritional management of cancer patients (especially those patients undergoing aggressive or palliative therapy) including feeding behavior, their alteration by disease and/or treatment and restoration toward normal feeding.

4. Studies for new approaches to the rehabilitation problems of head and neck cancer patients in relation to cosmesis, speech, and swallowing. These approaches may involve new materials and procedures, as well as new uses of existing approaches and procedures.

5. Studies for the development of new physical techniques/procedures to rehabilitate cancer patients with specific deficits (paraplegia, stoma, etc.) to the extent that these techniques are of primary benefit to cancer patients.

6. Studies for the development of new concepts and procedures for the continuing care of cancer patients with the disease in varying states of control.

7. Studies of social factors in relation to the patterns of rehabilitation and continuing care to include level of care received, impact of care and of alternative approaches for the patient, family, and community, including health professionals.

Special Community Resource Development

Under this general area of cancer control, applications are to be concerned with the development of

community outreach programs through NCI's designated comprehensive cancer centers and multi-protocol clinical cooperative groups.

DCC&R is not involved in performing regulatory activities, nor does it support delivery of health care per se. Neither does it support the usual laboratory and clinical research to develop new techniques and procedures.

The grant program is not intended to duplicate contract programs of the division, and applications duplicating current RFPs or existing contract programs will be returned. Because exceptions may exist, NCI advised potential applications to consult with DCC&R staff to determine if a proposed study will fit within the above guidelines.

Goal of the Cancer Control Program is to reduce the incidence, morbidity and mortality from cancer through:

1. Identification of new methods, knowledge, and techniques that may be applicable to control activities.
2. Field testing of potential control knowledge and techniques in limited community field trials to determine their potential for widespread community usage.
3. Evaluation of potentially useful control knowledge and techniques to determine their effectiveness, practicality, acceptability, impact on the disease, and economic or cost-benefits prior to embarking on costly widescale community demonstration and promoting efforts.
4. Demonstration of effective, practical, control knowledge and techniques.
5. Promotion of demonstrated effective, practical knowledge and techniques to assure their rapid widespread utilization in all areas in the nation.

DCC&R is concerned with the entire scope of the cancer problem, from the prevention of the disease to the rehabilitation and continuing care of the cancer patient during and after treatment.

Applications should be submitted on PHS grant application form NIH 398 which should be mailed to: Division of Research Grants, National Institutes of Health, Bethesda, Md. 20014.

Applicants should type "CANCER CONTROL" in the top margin of the application's face page. A covering letter should also identify the application as a response to the Cancer Control Program. A copy of this letter and any inquiries should be directed to:

Dr. Dorothy R. Brodie
Program Director for Grants
Division of Cancer Control & Rehabilitation, NCI
Blair Building – Room 628
NIH
8300 Colesville Rd.
Silver Spring, Md. 20910
Telephone: 301-427-7990

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 NCI-CP-65731-62

Title: *Professional and technical pathology support to the carcinogenesis intramural and extramural programs.*

Deadline: *Oct. 2*

This will include, as necessary, tissue processing, slide preparation and staining, and histopathologic diagnoses. It will also include interpretation, definition and classification of tumors and related lesions through the use of special stains, hosto-chemical, electron microscopic studies, transplantation and other procedures as necessary.

The pathologists will assist in the selection and coding of lesions for entry into the registry of experimental cancers, serve as consultants to the tumor pathology section and participate, as requested, in advisory panels, workshops, seminars and site visits.

It is expected that there will be frequent communication between the contractor and the NCI staff and it would thus be advantageous for the contractor to be geographically located near NCI. Alternate methods of establishing and maintaining effective communications with the NCI can be proposed for applicants distant to Bethesda.

Contracting Officer: D.J. Dougherty
Cause & Prevention
301-496-6496

RFP NCI-CB-63997-34

Title: *Epidemiologic characteristics of medullary and lobular breast cancer*

Deadline: *Dec. 20*

NCI is interested in establishing a contract for studies of the epidemiological characteristics of medullary and lobular breast cancer. Such studies should compare risk factors for less common defined morphologic types, such as lobular and medularry cancers with the more common infiltrating ductal type which comprises approximately 80% of breast cancers in the United States.

If possible the design of the study should also facilitate defining epidemiological sub-entities which might not necessarily correspond with exclusively defined histological types. The proposal could originate from one or a number of collaborating institutions.

RFP NCI-CB-63995-34

Title: *Epidemiology of non-invasive breast disease*
Deadline: *Dec. 20*

NCI is interested in establishing a contract for the study of epidemiology of non-invasive (benign) breast disease. The studies formulated should aim at establishing the epidemiologic features of benign breast diseases and should specifically include determination of the relevance of these to the established risk factors for breast cancer. The proposal could originate from one or a number of collaborating institutions.

RFP NCI-CB-63996-34

Title: *Definition of epidemiologic characteristics of pre and post menopausal breast cancer*
Deadline: *Dec. 20*

NCI is interested in establishing a contract to define epidemiological characteristics of pre- and post-menopausal breast cancer. The major objective is to determine whether breast cancer developing in women prior to the menopause has a similar spectrum of risk factors as breast cancer development in women following a natural menopause.

Studies may be retrospective (case control) or prospective (cohort), but should encompass a sufficiently large population, such that the epidemiological characteristics in both groups of interest may be defined with precision. Studies may be conducted within established high or low risk populations or across socio-cultural groups with different risk levels. The proposal could originate from one or a number of collaborating institutions.

RFP NCI-CB-63999-34

Title: *Studies of breast cancer incidence in populations exposed to repeated mammography*
Deadline: *Dec. 20*

NCI is interested in soliciting proposals from organizations having access to female populations that have had breast mammography on a regular basis for over 20 years. The primary objective is to determine the occurrence as well as the present incidence of breast cancer in these populations for comparison with the occurrence and present incidence in similar control groups. The population groups should be large enough so that statistical evidence of any excess in the occurrence and incidence of breast cancer relative to repeated mammography can be deduced.

Also of importance is the ability to determine breast cancer incidence rates at the beginning of and during the 20 year or greater period during which the population has been receiving mammography, for both study and control groups.

Contract Specialist (for above four RFPs):

E.J. Abbott
Biology & Diagnosis
301-496-5565

VIRUS CANCER PROGRAM REPORT ON SCIENTIFIC ACTIVITIES CONCLUDED

The report on scientific activities of NCI's Virus Cancer Program, which appeared in four previous issues of ***The Cancer Letter***, is concluded here with progress highlights not covered in the previous sections.

Type C RNA Viruses

Radioimmunoassays using antiserum to the RD114 cat virus and RLV p30 antigen detect a class of interspecies determinants common to murine, feline and non-human primate viruses. Antigen with the same apparent affinity for antibody as that of the interspecies determinants of the highly purified p30 RLV core protein was found in relatively high concentrations in the tissues from patients with systemic lupus erythematosis, and in lower concentration in some neoplastic tissues and in normal human tissues. The competing protein extracted from the spleen of a lupus case, chromatographed on phosphocellulose, was similar in gel filtratration characteristics to known p27 - p30 viral proteins.

The cytotoxic action of a monospecific antiserum for FLV gp71 against human myelogenous leukemia cells suggested the presence of cross-reacting cell surface antigens. The cytotoxic reaction could be blocked by gp71 and by the positive target cells but not by normal or lymphatic leukemia cells.

Cytoplasmic particulates recovered from quantities of acute myeloblastic leukemia cells contain a reverse transcriptase activity, but do not resemble virions morphologically. The reverse transcriptase from these particulates was shown to exist in two interconvertible forms of molecular weights 70,000 and 150,000. Since the two forms differ in their biochemical characteristics, interconvertibility may be associated with some regulatory function of polymerase activity.

Studies on terminal deoxynucleotidyl transferase in humans have shown that this enzyme is an extremely good marker for cells from acute lymphoblastic leukemia. Normal people have the enzyme only in their thymocytes and, at low levels, in the bone marrow. Three forms of the enzyme have been identified: two forms which are found both in thymocytes and in actue lymphoblastic leukemia cells and one form which has thus far been found only in the bone marrow.

By several criteria, including nucleic acid sequence homology and antigenicity of the polymerase and the p30 protein, the various baboon viruses are related to, but distinct from, the endogenous cat viruses of the RD-114/CCC group. The unexpected relatedness of the endogenous cat and the endogenous baboon viruses suggests that they have a common origin. Although all members of the cat family Felidae are closely related as shown by hybridization of their cellular DNA, only four species of the genus Felis

(domestic cat, sand cat, and European wildcat) contain endogenous virogenes related to the RNA of RD-114. However, all Old World monkey and ape species examined have nucleic acid sequences related to RD-114. These findings suggest that viral genes from primates gave rise to infectious particles that integrated into the DNA of an ancestor of the domestic cat and have since been transmitted as cellular genes. By examining the divergence time of the various species discussed above, this infection is believed to have occurred about 5-7 million years ago in the Mediterranean basin.

Antigens related to the major structural protein (p30) of baboon type C viruses have also been detected in normal baboon, rhesus monkey, and stumptail monkey tissues, and more recently, in several human tumors. These results indicate that humans, like other primates, contain endogenous type C virogenes in their DNA which can, in certain circumstances, be at least partially expressed.

It is characteristic of endogenous type C viruses that all individual animals of a species and all tissues of each animal contain nucleic acid sequences in the chromosomal DNA that code for the production of complete type C viral particles. Each species contains multiple (5-15) copies of endogenous virogene sequences per haploid genome, but heterologous species infected with and producing high titers of these type C viruses contain fewer copies (1 or 1 per haploid genome). The presence of multiple copies of viral information is thus a useful criterion with which to identify the species of origin of an endogenous mammalian type C virus.

More evidence has accumulated showing that viruses passaged through heterologous species lines, however briefly, pick up not only nucleic acids but also proteins of the new species. Thus, hamster viruses passaged through mouse and rat lines contain not only rat, mouse and hamster RNA sequences but also mouse, rat and hamster viral proteins.

The Kirsten and Harvey strain of sarcoma virus (which were each isolated by passage of MuLV in rats) contain genetic information not present in either the Kirsten strain of leukemia virus or the Moloney strain of leukemia virus. The additional information present in the Kirsten and Harvey viruses comes from rat cells and is present in normal rat cellular DNA. Apparently, the rat genetic information present in the Kirsten virus is the same as that in the Harvey virus, but it is unresolved whether the new rat genetic information is of cellular origin or derives from a distinct type C virus in rats different from the known rat type C viruses.

The gibbon virus was shown to cross-hybridize with hamster viruses in addition to its previously reported cross-hybridization to mouse viruses. This raises the question of whether the gibbon virus and the woolly monkey virus are not examples of viruses which have undergone reassortment under natural conditions.

Analyses of the RNA of viral recombinants led to the conclusion that genetic recombination among avian RNA tumor viruses involves molecular crossing over.

Four new genes affecting virus replication and tumor incidence have been described in the mouse, thus providing more evidence for the critical role of genetics in cancer.

Soluble extracts of mouse cells with Fv-1^n or Fv-1^b genotype inhibit infection by B or N-tropic mouse leukemia viruses respectively. The agent responsible appears to be an RNA molecule that affects some early step after penetration.

The stimulation of Type C virus production by dexamethasone and inhibition by interferon was shown to be a post-translational effect on the gene expression of RNA tumor viruses. It was found that this treatment did not alter the amount of intercellular viral protein, suggesting that dexamethasone and interferon act at the step after the viral proteins are synthesized, perhaps at the assembly of virus particles.

Most cellular DNA polymerases from several sources (e.g., nonactivated AKR cells, normal mouse spleen) have no affinity for poly(Um)-Sepharose columns at low salt concentrations. Reverse transcriptase (from RLV, AKR virus, activated AKR cells, or RLV-infected spleens) binds to the column and can be eluted with an NaCl gradient, leading to separation of the viral enzyme from most cellular DNA polymerases.

NZB mice produce large amounts of endogenous xenotropic virus early in life and correspondingly large amounts of immune globulins which form antigen-antibody complexes. Such complexes interfere with normal functions of the kidney and bone marrow, thus simulating the lupus-syndrome in man. Azathioprine immunosupression of NZB mice during early life leads to early lethal leukemias, lymphomas and sarcomas, a finding that demonstrates not only the importance of immune responses in the control of the cancer also rather strongly suggests that the large amounts of the xenotropic virus present in the leukemic tissues may be the actuating cause of the leukemias.

Antibody-dependent lymphocyte cytotoxicity may play a role in immunity directed against tumors induced by the Moloney sarcoma-leukemia virus complex. The sera from mice in which tumors had regressed actively mediated the destruction of Moloney virus-producing cells by normal or immune lymphocytes.

The high incidence of neoplasia in human organ graft recipients stimulated related studies in murine systems. It was observed that Type C RNA virus was activated by the graft versus host reaction leading to the development of malignant lymphoma in as many as one-half of the animals. Treatment with interferon inhibited virus activation and prevented development of lymphomas. Immune supression in animals receiving skin grafts from animals even with only minor hist-

ocompatibility differences considerably increased virus activation in comparison to either treatment alone.

Five chemicals and three biologicals capable of stimulating host immune responsiveness have been tested in mice for use as immunoadjuvants against several leukemia and carcinoma tumor systems in combined modality therapy studies. Of the five chemicals, levamisole has been examined in depth. The activity of this chemical immuno-adjuvant is expressed by stimulating the T-lymphocyte population. The effectiveness of levamisole as an immunoadjuvant in chemotherapeutically-induced remissions of leukemias and carcinomas has led to its incorporation into clinical protocols designed to treat human leukemia and colorectal adenocarcinomas.

Type B RNA Viruses

Three groups have independently shown that human leukocytes that are reactive against human breast cancer cells are also reactive in migration inhibition assays against mouse mammary tumor virus but not against type C mouse viruses.

Radioactive DNA (^{3}H-CDNA) complementary to the RNA of Mason-Pfizer Monkey Virus was used in molecular hybridization experiments to demonstrate sequence homology between MPMV RNA and RNA of human malignant breast tumors. Hybridization products were analyzed by cesium sulfate equilibrium density centrifugation and hydroxyapatite chromatography. Twenty-seven of 39 human malignant breast tumors tested contained MPMV-related RNA while no sequence homology was found in RNA from human benign breast tumors or normal breast, spleen, liver or kidney.

Successful supression of MuMTV expression and tumorigenesis by immunization with MuMTV has been accomplished. Two mouse strains, Af/C57BL and RIIIf/C57BL, were immunized with killed MuMTV in complete Freund's adjuvant. Expression of MuMTV up to the 10th lactation was significantly suppressed and tumor incidence at 15 months of age was reduced.

Infection and replication of MuMTV was obtained when a cat kidney cell line was exposed to the virus. No morphological difference was observed in the infected cells. Typical type B particles were recovered from supernatant fluids of cat kidney cultures serially passaged over 12 months. Virus production was also confirmed by membrane immunofluorescense.

A virus induced to replicate in guinea pig cells by exposure to halogenated pyrimidines has been shown to be related to the mouse mammary tumor virus. This close relationship has been demonstrated by similarity in ultrastructure and mode of replication, by identical density and by the presence of a reverse transcriptase preferring Mg^{++} instead of Mn^{++} in the reaction mixture.

DNA Viruses

A genetic contribution to the etiology of nasopharyngeal carcinoma (NPC) was indicated by studies in Singapore which showed that NPC patients and their relatives have an HL-A antigen on their leukocytes which is rarely detected in non-Chinese or in Chinese control patients.

Using tumor sections from nasopharyngeal carcinomas, in situ hybridization methods have provided strong evidence that EBV DNA is located in the malignant epithelial cells. Also, recently the carcinoma cells, freed of lymphoid cells by passage through "nude" mice, were shown to contain virus DNA and EBNA antigen.

When mouse cell cultures (JLSV-O) chronically infected with Rauscher murine leukemia virus were superinfected with HSV-1, the HSV progeny produced syncytial lesions on chicken embryo fibroblasts in contrast to the round cell plaques produced by the parental virus stock. The HSV variant is lighter in cesium chloride gradients than the parental stock and preliminary experiments show differences between the two DNAs. Of further interest is the ability to isolate viable Vero cell clones after infection of the cells by the syncytium-producing virus whereas this has not been possible with HSV-1 parental stock. These clones offer an opportunity to determine which HSV DNA fragments may persist within the cells and may provide a DNA probe for the examination of malignant human cells for the presence of HSV genetic information.

Co-carcinogenesis

RLV antibody specifically protects against malignant transformation by 3-methylcholanthrene in a well established rat cell culture chronically infected with RLV. Not only is transformation prevented but the RLV in the chronically infected cells is reduced to almost undetectable levels. RLV infected but antibody untreated cultures are readily transformed by the co-carcinogens; the use of antisera to unrelated RNA tumor viruses failed to protect.

Use of RadLV in low dosage as a live virus "vaccine" in three experiments in C57BL/6 mice resulted in significant reductions in the incidence of subcutaneous and intramuscular fibrosarcomas induced by 3-methylcholanthrene.

Significant enhancement of transformation by chemicals and papovaviruses has been described in otherwise stable rat cells following derepression of endogenous rat type C virus expressions by IdU prior to chemical treatment. Endogenous xenotropic viruses can, therefore, also serve as a cocarcinogen.

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