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DCT TO ANNOUNCE JUNE 1 GUIDELINES FOR CREG PROGRAM IN CELL KINETICS RELATED TO CHEMO, RADIOTHERAPY

NCI's Div. of Cancer Treatment will announce guidelines June 1 for its first cancer research emphasis grant (CREG) program, in cell kinetics related to chemotherapy and radiotherapy. The division has committed for the first year $200,000 to the program, which will involve the re-competition of existing DCT contracts in those fields; two to three grants probably will be awarded.

NCI has set aside $10 million in the fiscal 1976 budget for CREG. If the new funding mechanism proves to be successful, the CREG budget will be substantially larger in subsequent years. NCI executives have little doubt that it will succeed; HEW headquarters held the limit to $10 million the first year.

CREG was developed to stimulate research proposals in areas which NCI feels are ripe for exploitation while avoiding the "targeted" or "directed research" taint that is associated with contracts. The guide-

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In Brief

NCI GRANTS UP FOURFOLD SINCE 1970; RAPPAPORT, JENSEN SPEAKERS AT ANNUAL AACR/ASCO MEETING

NCI'S GRANTS program went from $93 million in 1970 to more than $280 million in 1974, John Kalberer, acting associate director for program planning in the Div. of Research Resources & Centers, pointed out in an article in the March issue of *Cancer Research.* Grants account for more than 50% of NCI's extramural research budget, Kelberer wrote. Increased funds have stimulated a large increase in new cancer applications, and young investigators have competed well for the additional money. . . . **HENRY RAPPAPORT,** City of Hope, will deliver the sixth annual David A. Karnofsky Memorial Lecture at the joint annual meeting of the American Assn. for Cancer Research and American Society of Clinical Oncology in San Diego next month. His topic will be "The Role of the Pathologist in Oncology." Elwood Jensen, Univ. of Chicago, will give the G.H.A. Clowes Memorial Lecture on "Hormone Dependency of Malignant Tissues." The Presidential Address, by Van Rensselaer Potter, is titled, "Humility with Responsibility: An Ethic for Oncologists." The meeting is scheduled May 7-10. . . . **MORE DETAILS** on NCI plans to follow up the work of Robert Gallo and associates in the isolation and complete biochemical and immunological characterization of a complete virus from the lab grown cells of a patient with acute myelogenous leukemia: NCI will fund increased efforts for confirmation by other labs, extension the work to other human leukemias, seeking similar viral isolets and production of the AML human virus. Most of this work will be through contracts and will involve the Frederick Cancer Research Center for production of the human virus.

DEVITA EXPLAINS NEW CLINICAL RESEARCH CONTRACT REVIEW RULES

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lines will outline the parameters of the problem, and investigators will be asked to develop their own approaches to the solution.

The Div. of Cause & Prevention is preparing guidelines for its first CREG program, to develop new or improved methods for in vitro chemical carcinogen testing (*The Cancer Letter*, March 21). Other CREG programs are being worked up in nutrition, viral oncology and immunology.

Meanwhile, the contract is still the dominant mechanism used by the program divisions. The DCT Board of Scientific Counselors heard a review of the division's contract programs at its recent meeting, including some hints about future RFPs.

DCT Director Vincent DeVita explained the new contract review procedures that will go into effect for the division at the start of the 1976 fiscal year, next July 1. Research contracts will require peer review by committees made up of at least 75% outside (non-government) scientists. Resource development contracts will be reviewed by standing committees of NCI staff members, with an annual review by the DCT Board of Scientific Counselors of program areas to be supported by contracts.

Research programs suitable for CREG will be identified by the cancer treatment program staff (CTPS), funds allocated and proposals initiated. Proposals will be reviewed by study sections. This will be investigator directed research and will not require an NCI project officer.

DeVita grouped program directed research contracts into three categories—clinical trials research, other program directed research, and equipment development.

The CTPS will identify clinical trials program needs and will initiate proposals. A project officer will be required to assure that protocols meet program needs. The contract will require the clinical best effort on a day to day basis by the investigator.

Peer review necessary in clinical trials program development or review of proposals, or both, will include annual review by the Board of Scientific Counselors with primary review by clinical trials review committees. If the program development approach has received peer review by the Board, review may be accomplished by an NCI standing committee, at the discretion of the director, deputy director or appropriate associate director.

Other program directed research contracts will require primary review by a developmental therapeutics review committee, with annual program review by the board.

Equipment development contracts will require only review by an NCI standing committee, with the annual review by the board.

Deputy Director Stephen Carter discussed the two major clinical thrusts of the division—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," Carter said. "This conflict is most critical in allocating clinical resources in the advanced disease states of different tumors. For each tumor, phase II resources may be used for investigating single agents, combination chemotherapy regimens, or even combined modalities. Single agents include established drugs that have not been tested against a given tumor, new schedules of established drugs, or investigational drugs. Investigational drugs may be those with some measure of established activity (e.g., nitrosoureas, adriamycin) or new drugs for which phase I study has recently been completed.

"Each tumor must be analyzed from the standpoint of what is required to develop an overall strategy for specific treatment. The drugs or regimens that are chosen for phase II and III study in patients with advanced disease must integrate into this strategy. However, in many cases the strategy may directly conflict with the needs of a drug development program which places as many as 10new drugs each year into clinical trial.

"Currently, there are approximately 25 commercially available standard antitumor agents. The drug liaison and distribution section holds INDs for more than 50 anticancer drugs. . . . The program currently has 10 drugs in phase I study and approximately 40 drugs that have passed decision network 2 in the linear array and are progressing toward eventual clinical trial. Since the input to the screen has been increasing, even the use of all the currently available clinical resources would be inadequate to meet the needs of the drug development linear array. Obviously, all the clinical resources cannot be sued in this way and it is essential that an overall strategy be designed for using these precious resources. The DCT must make decision in two critical areas:

"1. How many of the major solid tumor types will be included in the program and what priority should they have among themselves and in relation to ongoing programs in leukemia and lymphoma?

"2. How should the DCT allocate advanced disease resources, within the major solid tumors, between phase II studies of new investigational drugs and other single agents or combination regimens? As a result of this kind of analysis, a decision must be reached on the number of new drugs arising from the drug development pool that can be handled. Lastly, and most difficult, is the question of how many drugs

are actually best within the DCT overall treatment plan."

Carter reported on the division's clinical contract program.

"A phase I working group was formed about two years ago for the specific purpose of undertaking all initial clinical evaluations of drugs sponsored for clinical trial by DCT. The group has 11 member institutions, seven of which are funded to a total of $850,000.

"The group meets four times each year to present results of current studies and to obtain information about new drugs available for study. An attempt has been made to have this group interact with the critical individuals working in preclinical drug development so that the latter can understand the clinical needs and problems and modify their studies accordingly where possible.

"Lung cancer studies are supported by a series of contracts with individual institutions, either as part of an overall group or as independent investigators. In addition, a significant part of the Veterans Administration Cooperative Group work under the transfer of funds mechanism is involved in lung cancer studies.

"Large bowel cancer is the area in which the first clinical contract was undertaken by DCT nearly five years ago with the Mayo Clinic and Charles Moertel. This contract produced phase II evaluations of a large number of single agents, but, with the preliminary success of the methyl CCNU + 5-FU + vincristine combination and the tantalizing observations with MER, work has moved more into the phase III area. It is hoped that the phase II large bowel studies will be picked up by other contractors, especially the large solid tumor contractors. Combined modality studies will now become a major effort through a new RFP that will be integrated into the Gastrointestinal Tumor Study Group [proposals are now being evaluated by NCI].

"The contract interest of DCT in breast cancer is second in age only to large bowel cancer. Over the last few years these contracts have been fully integrated with the treatment contracts of the Breast Cancer Task Force since the project officers have been nearly identical in both cases. For this reason, DCT work in this area appears relatively smaller when compared to the other major tumor types.

"Pancreatic cancer was the first tumor type approached by the Gastrointestinal Tumor Study Group which was formed about 2½ years ago to develop combined modality trials for the entire range of gastrointestinal cancer. The organization concept for this group was to have a small highly selected group of institutions, each of which would send a member for each modality to plan trials for every stage of each disease type. The group studies in pancreatic cancer include seven funded contracts at a total cost of approximately $800,000.

"Stomach cancer, still a major killer in the United States despite its declining incidence, has been relatively neglected in the clinical trials area. The major thrust in DCT is through the Gastrointestinal Tumor Study Group in three on-going protocols, one for each stage of disease, with six contracts funded at a total yearly cost of $660,000.

"Until recently, contract-supported worked in ovarian cancer was relegated to the phase II-III area with two contracts totalling $220,000. Because of the excellent potential for a successful combined modality attack on this disease, an ovarian cancer study group will be established from a selected group of institutions with extensive experience and combined modality expertise to design trials which could not be done in a single institution. Approximately $1 million has been allocated to support this effort.

"Brain tumor studies are performed totally by the Brain Tumor Study Group which was the first contract supported group established by the former chemotherapy program.

"Testicular tumor trials are supported by a Testicular Tumor Study Group formed to conduct combined modality studies for stage II disease.

"Studies in advanced malignant melanoma will be supported through the large solid tumor contracts and those in early disease will be conducted by the WHO Melanoma Study Group.

"The remainder of the solid tumors will be studied through the large phase II-III disseminated solid tumor contracts, of which three have been approved to date. A search for more is planned."

OMB BACKS DOWN, MAY RELEASE FUNDS FOR CONSTRUCTION AT UCLA, SALK, NYU

Release by the Office of Management & Budget of funds for major new construction projects at three cancer centers "seems likely," NCI Director Frank Rauscher told the President's Cancer Panel Tuesday.

OMB has balked at releasing the money, totaling more than $9 million, because of White House opposition to funding any new construction of health facilities. But NCI has carried on a months-long argument with OMB over the issue, and was able to enlist the support of Asst. Secretary for Health Theodore Cooper and HEW Secretary Caspar Weinberger.

The pressure and/or sales efforts apparently have forced OMB to back down, as it previously did in a vain effort to block new construction funds for Columbia Univ. and Albert Einstein. Rauscher told the Panel the final OMB decision was due any time this week.

UCLA is the major beneficiary, with $5,062,500 for construction of its new cancer center. UCLA researchers and cancer clinicians have been forced to rent high-rise office space for labs and outpatient cancer clinics. Patients had to walk or be pushed in wheelchairs two blocks to the main medical center for x-ray and lab examinations.

The policy by OMB of supporting only renovations

to existing structures could not be implemented by UCLA—no structure capable of renovation for the new cancer center was available.

Salk Institute will receive $1.8 million approved by the National Cancer Advisory Board for new construction. New York Univ. was approved for $3.4 million, $1.3 million of which is for new construction with the balance earmarked for renovation and thus not challenged by OMB.

NCI Executive Officer Calvin Baldwin pointed out that OMB's release of the funds for UCLA, Salk and NYU does not mean the White House has dropped its opposition to new construction. The fate of more grants which will be acted upon by NCAB at its June meeting is still undetermined.

COOPER, FREDERICKSON FORMALLY NAMED BY FORD TO TOP HEALTH, NIH POSITIONS

President Ford finally made it official this week—he sent to the Senate the nomination of Theodore Cooper as Asst. Secretary for Health, and appointed Donald Frederickson director of NIH.

The White House leaked news of the appointments several weeks ago. Cooper will not have any problem in being confirmed by the Senate. He was director of the National Heart & Lung Institute from 1968 until last year, when he became deputy to Asst. Secretary for Health Charles Edwards. Cooper has been acting assistant secretary since Edwards resigned in January.

Frederickson preceded Cooper as director of NHLI, assuming that position in 1966. He elected to return to research in 1968 as chief of the Molecular Diseases Branch and later became director of NHLI's intramural research. He was named president of the Institute of Medicine last year.

CONTRACT AWARDS

Title: Continuation of pharmacology study of anti-leukemic and other anti-cancer drugs
Contractor: Southern Research Institute, $75,833.

Title: Preparation and purification of viral components
Contractor: Pfizer, Inc., $30,000.

Title: Isolation, propagation, and storage of mutant vertebrate cells
Contractor: Ontario Cancer Institute, $374,000.

SOLE SOURCE NEGOTIATIONS

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

Title: Cellular immunity studies to herpes simplex associated antigens in cancer patients and controls
Contractor: Emory Univ.

Title: Large-scale tissue culture virus production for cancer research
Contractor: Pfizer Inc.

NCI ADVISORY GROUP MEETINGS FOR MAY

Cancer Control Grants Review Committee—May 5–6, 9 a.m., Bldg 31 Conference Room 8. Open: May 5, 9–9:30 a.m.
Institutional Fellowship Review Committee—May 12–16, Bethesda Holiday Inn, open each day 8:30–9 a.m. Subcommittee on Epidemiology and Radiation, Diagnosis & Therapy, May 12; Subcommittees on Viral Oncology & Chemotherapy, May 13; Subcommittees on Drug Development and Immunology, May 14; Subcommittees on Tumor Biology and Carcinogenesis, May 15; full committee, May 16.
Recombinant DNA Molecule Program Advisory Committee—May 12–13, 9 a.m., Bethesda Holiday Inn, all open both days.
Cancer Control Support Services Review Committee—May 12, 8:30 a.m., NIH Bldg 1, Wilson Hall. Open: 8:30–9 a.m.
President's Cancer Panel—May 13, 9:30 a.m., Bldg 31, Conference Room 8. Open: 9:30 a.m.–12 noon.
Cancer Control Intervention Programs Review Committee—May 14, 8:30 a.m., Bldg 31 Conference Room 8. Open: 8:30–9 a.m.
Cancer Special Programs Advisory Committee—May 15–16, 8:30 a.m., Bldg 31 Conference Room 8. Open: May 15, 8:30–9:30 a.m.
Virus Cancer Program Scientific Review Committee A—May 16, 8:30 a.m., Bldg 31 Conference Room 4. Open: 8:30–9 a.m.
Cancer Research Center Review Committee—May 16–17, 8:30 a.m., Linden Hill Hotel, Bethesda. Open: May 16, 8:30–10 a.m.
Subcommittee on Environmental Carcinogenesis—May 17, 10 a.m., O'Hare Hilton Hotel, O'Hare Airport Room 2109, Chicago. All open.
Committee on Cancer Immunobiology—May 19–20, 9 a.m., Landow Bldg Room C-418. Open May 19, 9–9:30 a.m.
Subcommittee on Centers—May 21, 9 a.m., Bldg 31 Conference Room 4. Open: 9 a.m.–3 p.m.
Cancer Clinical Investigation Review Committee (Potomac Conference)—May 22–24, 8:30 a.m., Bldg 31, Conference Room 6. Entire meeting is open.
Cancer Control Support Services Review Committee—May 27, 8:30 a.m., Bldg 31 Conference Room 4. Open 8:30–9 a.m.
Molecular Control Working Group—May 28, 9 a.m., Bldg 31 Conference Room 7. Open: 9 a.m.–12:30 p.m.
President's Cancer Panel—May 29, 9:30 a.m., Bldg 31 Conference Room 8. Open: 9:30 a.m.–noon.
Committee on Cancer Immunotherapy—May 29–30, 8:30 a.m., Landow Bldg Room C-418. Open: May 29, 8:30 a.m.–2 p.m., May 30, 8:30 a.m.–adjournment.
Cancer Control Intervention Programs Review Committee—May 30, 8:30 a.m., Bldg 31 Conference Room 8. Open: 8:30–9 a.m.

MORE EXCERPTS FROM PAPERS PRESENTED AT ACS SEMINAR FOR SCIENCE WRITERS

Following are the last of the excerpts from presentations made to science writers at the seminar sponsored by the American Cancer Society. Other excerpts appeared in ***The Cancer Letter*** *the previous two weeks.*

ACS has a limited number of copies of most of these papers and will send them upon written request as long as they last. Write to ACS, Alan Davis, vice president-science writer, 219 E. 42nd St., NYC 10017.

BCG IMMUNOTHERAPY OF MALIGNANT MELANOMA: SUMMARY OF A SEVEN-YEAR EXPERIENCE – *Donald Morton, UCLA*

Evidence acquired over the past seven years has shown that manipulation of the immune system can favorably affect the clinical course of patients with malignant melanoma. A total of 151 patients were treated with immunotherapy using BCG alone or as an adjunct to surgical therapy. Immunocompetent patients with intradermal metastases who were treated with intratumor injections of BCG were the most likely responders to treatment. Of 45 patients treated with BCG vaccine, 36 had regression of 91%

of injected lesions. Six of these patients had regression of uninjected lesions as well. Eleven of the 36 remained free of disease from 6 to 74 months following BCG immunotherapy.

Patients with subcutaneous or visceral metastatic lesions had a poor response to BCG immunotherapy. Complete regression of uninjected lesions was not observed and none of these patients remained completely free of disease. However, results were improved significantly with palliative surgical resection followed by BCG immunotherapy although many patients developed recurrent disease.

COMPUTED AXIAL TOMOGRAPHY – ***William Marshall Jr., Stanford***

A new x-ray scanning technique easily reveals information about the inside of the body which was either unobtainable or expensive and dangerous to obtain.

Traditionally medical x-ray images are generated by passing an x-ray beam through the patient. The beam exiting from the patient contains a vast amount of information as to the densities in its path. Our methods of extracting this information, however, have been very inefficient. They generally employ film which is basically insensitive to small degrees of change (attentuation) in the beam.

The new device uses electronic tubes (photomultiplier tubes) rather than film. These tubes are quite efficient in measuring the differences in the exiting x-ray beam. This has been combined with a sectional or slicing (tomographic) method of looking at body structures and is now revolutionizing diagnostic radiology.

DEFECTIVE INTERFERING VIRUSES – ***John Holland, Univ. of California (San Diego)***

Alice Huang and David Baltimore in 1970 suggested the intriguing possibility that defective interfering particles might play a major role in the evolution of virus disease in man and animals. These DI particles are gene deletion mutants of infectious virus, and they all lack part of the entire DNA or RNA genome of the parental virus, hence they can grow only in cells which are also infected by infectious parental virus (to provide missing gene products). All types of human and animal viruses produce DI under appropriate circumstances, and these DI have the ability to interfere specifically with the growth of parental virus or closely related viruses. . . . Our recent work tends to validate the possibility that DI can alter virus disease in vivo. We have found that DI can be generated in vivo, that they can slow down acute fatal virus disease or even prevent death when *administered prophylactically at* the time of virus *infection, or when used to immunize before infection.* *Persistent infection with defective* virulent viruses may explain how such viruses might cause slowly-progressing persistent degenerative diseases in addition to the usual acute virus infections. For example, measles virus, in addition to causing the acute childhood disease is now implicated in a slowly progressing degenerative brain disease called subacute sclerosing panencephalitis, and it may be involved in multiple sclerosis and other degenerative diseases. It will be important to determine whether defective interfering particles play a role in these diseases, and to determine whether other chronic degenerative diseases including cancer involve persistent infection by defective mutants of viruses which have previously been thought to cause only acute infectious diseases.

ANIMAL VIRUS PSEUDOTYPES: WOLF IN SHEEP'S CLOTHING – ***Alice Huang, Harvard***

Viral genetic information may occasionally become packaged in proteins synthesized under the direction of another unrelated virus. When this occurs we get a pseudotype or, in other words, a wolf in sheep's clothing. The pseudotype has acquired temporarily the host range and surface properties of the donor virus. Such pseudotypes have a wide range of usefulness in biology and medicine. They may, also, indicate another mechanism by which viruses persist and spread. The author has demonstrated the extent of pseudotype formation among diverse groups of animal viruses.

ACCUMULATING EVIDENCE OF THE CANCER POTENTIAL OF HUMAN HERPESVIRUSES – ***Fred Rapp, Pennsylvania State Univ. (Hershey)***

Our laboratory has pioneered the attempts to determine directly the transforming activity of human herpes simplex and cytomegaloviruses. These ubiquitous viruses have been associated with a variety of human neoplasias by serologic and epidemiologic techniques.

Initial studies using inactivated virus revealed the rare transformation of hamster cells; though infrequent, these cells were malignant causing either fibrosarcomas or adenocarcinomas with metastases often to the lungs of the inoculated animals. However, the rarity of the transformation observed prevented quantitation and seriously hampered efforts to screen fresh isolates of these viruses for oncogenic properties.

Now, a focus forming assay in certain strains of mouse cells has been developed that will facilitate the detection and quantitation of the transforming potential of these candidate human tumor viruses. Within four weeks after exposure of a variety of 3T3 cells to inactivated herpes simplex virus type 1 or herpes simplex virus type 2, two types of morphologically distinct foci were observed; these represented both fibroblastoid and epithelioid transformants. *These results, coupled with the transformation of chicken, rat, and human cells by inactivated virus,* strengthen the hypothesis that these viruses have oncogenic capability. Use of virus mutants and even

fragments of herpesvirus DNA to transform a variety of cells are proving useful adjuncts in attempts to unravel the molecular mechanisms underlying the transformations observed. The techniques developed in these systems should be readily applicable to the quantitative transforming assay developed in our laboratory.

There are several important reasons contributing to the significance of a quantitative focus forming assay. It provides a valuable technique for evaluating the transforming potential of human isolates of herpes simplex viruses and perhaps cytomegalovirus, for indirectly evaluating the potential role of herpes simplex viruses in human cancer, for studying the interaction of RNA and DNA-containing viruses within transformed cells, and for determing the events regulating transformation and the mechanism of virus latency. Finally, the cells lines already developed after transformation with herpesviruses are proving extremely useful in efforts to develop technology to detect minimal quantities of virus nucleic acid, a problem that has seriously impeded efforts to resolve the issue of presence of herpesvirus genomes in human cancers.

HORMONES AND BREAST CANCER – ***Olof Pearson, Case Western Reserve***

Endocrine treatment provides effective palliation for about 40 percent of women with breast cancer whose tumors are dependent upon hormones for maintenance of growth. The most effective endocrine treatment consists of removal of endocrine glands (ovaries, adrenal glands or the pituitary gland) and less effective therapy consists of administration of pharmacological doses of hormones (estrogens, progestin, androgens and corticosteroids). With optimum treatment (hypophysectomy) tumor growth can be controlled for an average period of 18 months although in individual patients control may last for several years.

Progress in this field has been made in several areas. One of these areas is the measurement of hormone receptors in the breast cancer tissue for the purpose of predicting which patients have hormone-dependent cancers. . . .

We are also measuring other hormone receptors (Prolactin, progesterone, androgen) in tumor tissue to determine whether the presence of multiple receptors might further improve the predictability of hormone responsiveness of the tumors. . . .

In a collaborative study with Drs. Kathryn Horwitz and William McGuire of San Antonio, Texas we have measured progesterone receptors in human breast cancer tissue. . . . Clinical correlations have been completed in only 9 patients so far, but we hypothesize that the presence of progesterone receptors may be a more sensitive marker of endocrine dependence.

Another area of progress is knowledge about which hormones are most important in maintaining the growth of hormone responsive human breast cancer. . . . Studies in patients with breast cancer have shown that estrogens play an important role in maintaining the growth of hormone-dependent cancers, but after hypophysectomy estrogen by itself does not stimulate tumor growth which suggested that a pituitary hormone might also be playing a critical role. . . .

We have studied a new prolactin-inhibitor drug (Lergotrile mesylate, Eli Lilly Co.) in 12 patients with breast cancer. This drug effectively inhibits the secretion of other pituitary hormones. . . .

We are also investigating the therapeutic effectiveness of an anti-estrogen drug (Tamoxifen, ICI United States). In preliminary studies by others, approximately 35 percent of patients obtain remissions of their cancers with the use of this drug. . . .

Dr. Santos and his colleagues from Hershey, Pa. are attempting to develop a medical adrenalectomy with the use of two drugs (Aminoglutethimide and Dexamethasone). These drugs inhibit the biosynthesis of adrenal steroids. In preliminary studies, they have obtained remissions in 40 percent of a small series of breast cancer patients.

The goal of these studies is to eventually combine optimum endocrine therapy with optimum cytotoxic chemotherapy and immunotherapy in the hope of obtaining more effective control of breast cancer in women.

THE ROLE OF VIRUSES AS NATURAL TRANSMITTORS OF GENES BETWEEN SPECIES – ***G.J. Todaro, R.E. Benveniste, NCI***

In recent months considerable interest has been focused on the possibilities and risks associated with the introduction of new genes into the germ line of a species. Genes can be inserted into or deleted from bacterial viruses in the laboratory by simple chemical manipulation. But what is known about the natural role of viruses as transmittors of genes in higher organism?

In our laboratory in the past year we have developed evidence that shows that RNA tumor virus (type C virus) genes have been maintained as stable endogenous genetic elements in primates, including man, for at least 30-40 million years. Viruses from an ancestor of the modern Old World monkeys also could be shown to have entered the germ line of ancestors of the domestic cat. From the relatives of the domestic cat that have this virus and from those that did not acquire it, we have concluded that the infection occurred 3-10 million years ago somewhere in Africa or in the Mediterranean Basin region. Because of the stability of the viral gene sequences when they are incorporated into cellular DNA, events that have occurred millions of years ago still can be recognized by examining the genetic information of the virus and that of the host cell.

More recently, our laboratory has found a second example of gene transmission between species, in this

case from an ancestor of the mouse to an ancestor of the domestic pig. Peg cell cultures produce type C viruses that can be shown to be genetically transmitted and present in all pig tissues in multiple copies in the cellular DNA. Close relatives, such as the European wild boar and the African bush pig, have closely related viral genes in their DNA. It can be shown that this virus was acquired by an ancestor of the pig from a small rodent related to the mouse. We are also investigating other cases where the type C viruses have successfully introduced themselves into the genetic material of evolutionally distant species. That viruses can transmit themselves between the DNA of very different species has been established as a result of experiments in our own laboratory in the past year. That they can carry cellular gene sequences from cell to cell also has been clearly demonstrated. That this transmission of cellular gene information between species has been a major force in evolution remains a speculation without, at the moment, any direct proof.

TYPE-C RNA TUMOR VIRUSES DERIVED FROM HUMAN ACUTE MYELOGENOUS LEUKEMIA CELLS AND FROM OTHER PRIMATES – ***Robert C. Gallo, NCI; Robert C. Gallagher, NCI; S. Zaki Salahuddin, Litton Bionetics***

We isolated a type-C RNA tumor virus from newly cultured leukemic cells obtained from the blood of a patient with acute myelogenous leukemia (AML). Recently, we isolated the same virus again from a separate blood sample from the same patient at a later course of her disease. The isolation has been made possible by the identification of a factor from human embryo which promotes specifically the growth and maturation of human myelogenous leukemia cells.

Prior to the virus isolation, fresh blood cells from several patients with AML were shown to contain molecules related specifically to analogous molecules from these RNA tumor viruses isolated from leukemias and lymphomas of gibbon apes and from a sarcoma of woolly monkey. The isolated virus contains the same molecules, i.e., a reverse transcriptase and other viral proteins resembling proteins from the gibbon ape leukemia virus (GaLV) and from the woolly monkey (simian) sarcoma virus (SSV).

PREDICTION OF BREAST CANCER RESPONSE TO ENDOCRINE THERAPY – ***Elwood Jensen, Univ. of Chicago***

It appears that the determination of estrogen receptors in human breast cancers, both primary and metastatic, can furnish information useful to the clinician in his choice of the optimal therapy for the individual patient with advanced breast cancer. Of patients with significant tumor estrophilin levels, most, but not all, will respond favorably to endocrine therapy. Women whose cancers lack sufficient amounts of estrophilin have little or no chance of benefit from endocrine ablation or hormone administration and probably should be treated by alternative types of therapy.

EFFECTS OF PROLACTIN ON EXPERIMENTAL ANIMALS – ***Howard Bern, Univ. of California (Berkeley)***

The many biological effects of prolactin include its contribution to normal breast development and function and to the origin and growth of breast cancer in experimental mammals. Comparative studies of prolactin function may yield information on the chemical-structural basis for its growth-stimulating effect as opposed to its milk-stimulating effect and on the way in which this hormone acts on breast tissues.

PREDICTIVE MECHANISMS FOR RESPONSE TO ENDOCRINE ABLATION OR TREATMENT WITH HORMONES FOR PATIENTS WITH METASTATIC BREAST CANCER – ***William Fletcher, Univ. of Oregon***

There is a spectrum of possibilities developing from these studies. First, anti-estrogens might be used to select patients who might respond to endocrine ablation or blocking of the estrogen receptor by estrogen or other hormones. Second, anti-estrogens could serve as treatment in aptients who are not candidates for endocrine ablation. Third, it is documented that patients who have had removal of all estrogen secreting organs develop a new source of estrogen. This could come from the skin, from the liver, or conversion of exogenous drugs. In this case it is likely that the administration of anti-estrogens in patients who have responded to endocrine ablation could block a recurrence of the disease by binding with the ER and negating the effect of the recurrent estrogen. Fourth and finally, a complete understanding of how the presence of an estrogen receptor in the cancer cell relates to the coding of genetic information within and without the cancer cell is critical to the modern management not only of patients with cancer of the breast but may serve as a model for the study of patients with other endocrine sensitive tumors such as cancer of the prostate, thyroid, kidney, and andometrium.

CANCER VIRUSES IN THE INTERPHASE BETWEEN SELF AND NON-SELF – ***Richard Lerner, Scripps Clinic & Research Foundation***

Perhaps the most telling property of many cancer viruses is that they most often do not cause cancer. This is most clearly seen in mice such as the AKR in which all cells are infected, but only thymocytes become malignant in aging mice. In fact, if the thymus is removed from young mice cancer does not develop. Obviously, control over the malignant expression of viruses exists, and one of the primary goals of cancer research is to understand the nature of these controls.

This year, the widely held concept that the molecular mechanisms which contro the expression of virual genes are similar to those which control expres-

sion of the "normal" genes came into sharp focus by the finding of our group that the major C-type virus envelope protein is nearly identical to a normal cell marker, the expression of which accompanies certain cell differentiations. In fact, the amount of this marker protein in the serum of some normal mice exceeds that of some proteins responsible for critical life processes, such as blood clotting. Since the Mendelian inheritance of the cell surface protein had been defined, a similar mode of inheritance for the viral protein is implied. On further study, the relationship of this major C-type viral glycoprotein to its host became even more intriguing. We found that it is a secretion of epithelia cells of the mouse and as such, among other things, is "put" onto the head of sperm. All these findings point to the usefulness to the host of its symbiosis with viruses and underscore the probability that cancer may be an unfortunate accident in an otherwise natural balance. This exercise is more than academic for several reasons.

First, we can now explore how in different cells the host controls expression of a viral gene. Second, we can hope to study the normal secretions of man for expression of genes which potentially might lead to malignancy. Third, and of greatest significance, we may learn about the mechanisms by which cellular and those genes with extracellular potential interact in higher organisms.

RNA TUMOR VIRUS GENE EXPRESSION IN HUMAN TISSUE – ***J. Thomas August, Albert Einstein College of Medicine***

A problem of widespread interest is the possible role of RNA tumor viruses in human cancer. Infectious RNA tumor viruses are known to produce leukemia, lymphomas and sarcomas in a variety of animals but, to the present, there is little evidence that they infect and cause disease in man.

Recently, utilizing purified proteins from a variety of known RNA tumor viruses and immunochemical techniques, we demonstrated the presence of analogous proteins in human tissues. Several conclusions can be drawn from this work.

(1) Viral proteins were detected in each of several normal human tissues tested. This suggests that most, if not all, humans contain RNA tumor virus genes in their cells, either as endogenous viral genes, as occurs in other species, or as a result of widespread infection.

(2) In almost every case, 9 of 10, analysis of the character of the protein in the positive tissues showed that proteins analogous to those of both the wooly monkey/gibbon ape group and the baboon/RD 114 group of viruses were detected. Thus, humans appear to carry both of the currently known groups of primate RNA tumor viruses, either as endogenous or infective viruses. . . .

(3) No evidence was found for a unique "hu[illegible] group of RNA tumor virus. This suggests that su[illegible] virus, if it exists, is rare.

(4) Of the limited number of tissues examined, there were no significant differences in the concentrations of viral proteins in normal as compared to malignant tissues. This comparison requires extensive further analysis. The importance of the point is that the concentration of viral protein as a measurement of virus or viral gene products may be indicative of malignancy arising as a viral infectious process as compared to disease induced in some other manner.

(5) One apparent correlation was a markedly elevated level of viral protein in tissues of patients with systemic lupus erythematosus, an autoimmune disease. A possible role of RNA tumor viruses in the etiology of this disease has previously been suggested by the close correlation in mice of the occurence and severity of a lupus syndrome with the expression of an endogenous RNA tumor virus. The present findings provide evidence for a similar role in human disease.

GROWTH HORMONE AND BREAST CANCER – ***U.J. Lewis, Scripps Clinic & Research Foundation***

Some 30% of breast cancers can be maintained and actually stimulated to grow in vitro if pituitary growth hormone is supplied to the tumor. This work was done by J.R. Hobbs, Westminster Medical School, London, using our preparations. Portions of the tumors are placed in a nutrient medium either with or without addition of the hormone. If the tissue requires growth hormone for maintenance and growth, the treated samples will remain viable whereas the untreated tissue will die. The ultimate goal of the work is to determine if this laboratory observation has significance in development of the human disease, that is, does growth hormone play a role, either causative or supportive, in breast cancer.

GENETIC CONTROL OF TYPE C VIRUS IN WILD MICE – ***Murray Gardner, Univ. of Southern California***

We have shown that the indigenous type C virus is the cause of two naturally occurring diseases, 1) lymphoma and 2) a hind leg paralysis in wild house mice (Mus musculus). By cross-breeding the cancer/paralysis prone wild mice with a cancer resistant inbred mouse strain we have suppressed latent type C activity and have largely prevented both diseases in the progeny. Our findings underscore the importance of genetic factors and the possibility of their purposeful manipulation for control of type C virus associated diseases in wild mice.

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