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O'CONOR NAMED DCCP DIRECTOR, SAYS HE'LL PUSH DEVELOPMENT OF NCI'S EFFORTS IN EPIDEMIOLOGY

After a "world-wide" search, NCI Director Arthur Upton found the man he's been looking for to head the Div. of Cancer Cause & Prevention. It's Gregory O'Conor, who has been right there all along as acting director ever since Upton created the opening last September by firing James Peters.

Upton selected O'Conor from "six to eight" names he said were submitted by the search committee, names culled from a list of more than 100 presented to the committee, which was chaired by Div. of Cancer

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In Brief

ACCC LOBBYISTS GOT WHAT THEY WANTED IN HOUSE CANCER ACT BILL; VA GROUP REVIEW SET MAY 2

EFFECTIVE LOBBYING by Assn. of Community Cancer Center representatives was responsible for three provisions added to the Cancer Act renewal bill approved by the House Health Subcommittee last week: Requirement that at least two members of the National Cancer Advisory Board be practicing physicians actively engaged in treating cancer patients; spelling out authority for NCI support of continuing education for health and allied health professionals conducted by cancer centers; and including support for local and regionally-initiated education and demonstration programs as efforts that can be supported by NCI's Cancer Control Program. Robert Clark of Indianapolis is chairman of ACCC's legislative committee. . . . **REVIEW OF THE VA** Surgical Adjuvant Group demanded by NCI's Div. of Cancer Treatment Board of Scientific Counselors has been scheduled for May 2. The Board demanded that NCI's support of the Group be cut off if a review was not made. Because VASAG gets its NCI money through an interagency transfer agreement, which is basically a contract, it could not be reviewed by the Cancer Clinical Investigation Review Committee, which passes on grants for the other cooperative groups. The VA group gets about $2 million a year, which chairman George Higgins says is less than the group was getting in 1964 when it had three fewer participating hospitals than it has now (26). "If we can't get a little more support, we probably ought to fold up and do something else," Higgins said. . . . **ADJUVANT THERAPIES** and markers of post surgical minimal residual disease are the topics of a symposium sponsored by the European Organization for Research & Treatment of Cancer, June 22-24 in Paris. Cochairmen are G. Mathé, Paris; G. Bonadonna, Milan; and S. Salmon, Tucson. Contact A.M. Neukirch, ICIG, Hôpital Paul Brousse, 14-16 avenue Paul-Vaillant-Couturier, 94800-Villejuif, France. . . . **NATIONAL CONFERENCE** on Nutrition in Cancer, sponsored by ACS and NCI, is scheduled for June 29-July 1 in Seattle. Contact S. L. Arje, ACS, 777 Third Ave., New York 10017.

O'CONOR APPOINTMENT MEANS DCCP'S REORGANIZATION CAN NOW MOVE AHEAD

(Continued from page 1)

Treatment Director Vincent DeVita. Upton had said earlier that there were "some outstanding people" in that list, some from outside the U.S.

In making the announcement, Upton said, "The institute is extremely fortunate that Dr. O'Conor has agreed to assume this difficult position. His accomplishments in cancer research and his effective performance as both associate director for international affairs and acting division director have been amply demonstrated. We are most appreciative of his broad scientific and leadership abilities and his commitment to the National Cancer Program."

O'Conor, who will be 54 in June, told ***The Cancer Letter*** after he became acting director that he did not want the permanent appointment. "I meant it then and I'm still not sure why I agreed to take it," he said this week.

O'Conor is credited with doing a first rate job as head of the Office of International Affairs, a position he has held since 1973. The Cancer Act charged NCI with the responsibility for fostering and carrying out cooperation with foreign scientists. That part of the formal health agreements with other countries, most notably the USSR, having to do with cancer also has been in NCI's domain. NCI supports a fair number of research activities outside the U.S. In all of these, O'Conor's office has been required to participate one way or another.

In addition, the office includes the International Cancer Research Data Bank, another congressional mandate. ICRDB maintains files on all cancer research projects and protocols around the world and makes them available on request. The still developing Cancergram service will automatically send literature abstracts to scientists in their respective fields.

Why would O'Conor give up an interesting job like that for a politically sensitive one with an endless number of headaches? "You tell me," O'Conor laughed.

One answer might be that the DCCP position is a challenging one, and with the increasing emphasis on prevention can only increase in importance in the National Cancer Program.

Another might be that Upton, perhaps frustrated in an attempt to recruit someone outside the government, did a hard sell job on O'Conor. Upton has found that the top people he might consider the best qualified to run the NCI divisions are making too much money to be easily lured to Washington. All five divisions have changed directors since 1973; all five replacements came from NCI staff.

O'Conor, a native of Cincinnati, is certified by the American Board of Pathology in pathologic anatomy and clinical pathology. He joined NCI in 1960 and became involved in direction and supervision of the post mortem and surgical pathology services and the residency training program. In 1966, he was assigned by NCI to the World Health Organization, where he worked two years helping organize and develop the International Agency for Cancer Research. After his return to NCI, he headed the surgical pathology section in the Laboratory of Pathology, until taking the international affairs position. He will continue with that job until a new associate director is appointed.

O'Conor received his bachelor and medical degrees from Cornell. He took postgraduate training at New York Hospital, Univ. of Cincinnati Medical College and Cincinnati General Hospital, and St. Francis Hospital in Hartford. He has been chairman of the Commission on Epidemiology and the U.S. national committee of UICC and has been a member of the UICC executive committee.

DCCP encompasses four program areas: carcinogenesis research, carcinogenesis testing, viral oncology and field studies and statistics. The division spent $45 million in fiscal 1977, about 18% of NCI's $816 million budget.

As acting director of DCCP, O'Conor has been involved in the NCI reorganization but has had to leave a number of issues unresolved, agreeing with Upton that the permanent director should be in on those decisions.

A key issue—the fate and home of the Bioassay Program—is one that will be settled at a higher level, however. HEW is considering taking that program and moving it into some new office or agency to include most or all other toxicity testing. Some NCI executives would not mind seeing the routine carcinogenesis testing of chemicals go elsewhere; others argue that NCI will have to remain involved with testing in order to properly carry out carcinogenesis research.

Otherwise, the reorganization of DCCP now is free to move forward. The new setup probably will include these elements, O'Conor said:

—All extramural research will be totally removed from the intramural activities and placed under an associate director for extramural research.

—The intramural program probably will not have a scientific director heading it up. It will be run similarly to the Div. of Cancer Biology & Diagnosis, where the laboratory chiefs report directly to the director. "That's subject to modification later, but the lab chiefs prefer it that way and it provides for better interaction of the scientific activities," O'Conor said.

—There will be three branches in the extramural program—Biological Carcinogenesis (to include viral oncology); Chemical & Physical Carcinogenesis; and either Prevention or Special Programs.

A Prevention Branch probably would include the Smoking & Health and Diet & Nutrition Programs, retinoid research and some immunoprevention research.

"I hope we can do everything possible to see the epidemiology programs are given the opportunity to develop as broadly as possible so that NCI can assume its proper place as the focus for cancer epidemiology in the country," O'Conor said.

NCI NOT FOLLOWING CONGRESS MANDATE ON CANCER CENTERS, ZUBROD CONTENDS

The intent of Congress is clear—cancer centers were to be developed primarily to offer the best cancer care, to engage in cancer education, and to carry on outreach activities. "But NCI regards centers purely as research instruments. When we're reviewed for renewal of our grants, we're reviewed solely for our research," said Gordon Zubrod, director of the Florida Comprehensive Cancer Center.

Zubrod, 1977-78 president of the American Assn. for Cancer Research, expressed those views at a press conference during the recent AACR meeting. Nathaniel Berlin, director of the Northwestern Univ. Cancer Center and a former NCI colleague of Zubrod's, also participated in the press conference.

"In order to qualify as a comprehensive center, we have to meet 10 characteristics (established by the National Cancer Advisory Board). NCI funds only two of them," Zubrod said.

Berlin pointed out that the National Cancer Act of 1971 authorized NCI to support 15 comprehensive centers, funded at a maximum level of $5 million a year. When the Act was renewed in 1974, the limit of 15 was removed, and there now are 19 NCI recognized comprehensive cancer centers.

"Some could make the interpretation that NCI is not fulfilling the letter of the law," Berlin said.

"The centers program needs a vigorous spokesman and leader," Zubrod said. "It is the major technology transfer mechanism we have."

One of the major problems cancer centers encounter in conducting clinical trials is that "it is hard to get untreated patients into centers," Zubrod said. "A lot of people are getting care that does not save their lives. . . . My experience in Florida is that oncologists (in centers and in private practice) provide very good care. That's when patients do get into the hands of oncologists. The problem is before that."

The way to approach that problem, Zubrod said, "is to educate the whole profession on what they can handle, what they should refer."

Commenting on criticism that the Cancer Program was oversold in the process of getting it through Congress, Berlin said, "Progress is as great as scientists expected it would be then, but not as much as the public expected. No one anticipated any immediate major breakthrough, at least none at NCI nor did most of the cancer researchers."

Zubrod selected as the topic for his presidential address, "Selective Toxicity of Anticancer Drugs." Joseph Bertino, who delivered the Rosenthal Foundation award lecture, had a similar topic, "Toward Improved Selectivity in Cancer Chemotherapy."

"When I chose my subject for tonight's talk, the program committee had not yet gone to work," Zubrod said. "When they announced their program—and I congratulate Dr. (Enrico) Mihich and his committee for a splendid effort—I found that selective toxicity had come of age and that my topic, which by now had been made irreversible by the printer, was certain to be anticlimactic. . . . The splendid presentations this morning by Dr. Bertino and at the symposium (on the biochemical and pharmacological basis of chemotherapy) emphasis that it is now possible to design drugs with high selective toxicity and it is my fervent hope that much better drugs will come forth.

"I sometimes wonder if we haven't squeezed dry the trial of drug combinations based on empiric trial and error," Zubrod continued. "It reminds me a little of the era of super-radical surgery with ever more complexity and toxicity. The increasing incidence of induced leukemia and other second tumors following combinations is of growing concern that perhaps we have reached the limit of multicombinations. Combinations based on kinetic and pharmacologic realities represent a much more promising approach, and I believe that such reasoning will lead to simpler combinations of shorter duration with less toxicity.

"Multidisciplinary care with cure of local tumor by surgery or irradiation and cure of micrometastases by drugs has great promise for lowering cancer mortality. Its full exploitation awaits the better definition of subtypes of cancer and determination of the best chemotherapy for each subset. The study of human tumors in the nude mouse could provide the most rapid route for the selection of curative regimens for each subset.

"The three elements of importance in cancer chemotherapy are the host, the drug and the tumor. It is now possible to manipulate each of these three elements to increase selective toxicity. Manipulation of the host by immunologic means has not, to date, added to the ability to cure. For the distant future it would seem to hold promise, not perhaps so much for cure of established disease, as for cure of micrometastases. Supportive therapy such as the use of platelets, protection against infection, the remedying of physiological deficits, has played and continues to play an important role in decreasing the toxicity for the host. Rescue techniques, now limited to methotrexate, may have immense power in decreasing host toxicity if they can be extended to other drugs.

"Manipulation of the drug component through pharmacologic means has been of enormous help in increasing selective toxicity of drugs for the cure of infectious diseases. To date, it has been disappointing in its contribution to the cure of cancer. The reason for this is the fuzziness of the target. We cannot pose the critical questions to the pharmacologist until the target is considerably sharpened. The target

in infection is easy: malarial parasites were spontaneously synchronized; in pneumococcal pneumonia all the bacteria were dividing about every half hour. The cancer cell target will emerge from obscurity when we know the kinetics of each cancer subset. While this goal seems achievable for a few cancers, it will take a few years to accomplish this for all cancers.

"Increase in selective toxicity by manipulation of the tumor has also been disappointing. The failure is particularly keen for manipulation of the proliferating fraction. My personal conviction is that the potential contributions of cell growth kinetics to selective toxicity has been unrealized because of superficial application. Real study can begin only when highly defined subsets of cancer can be studied with modern kinetic techniques and then, at long last, with pharmacologic techniques."

Zubrod played a key role in the early development of cancer chemotherapy and was director of NCI's Div. of Cancer Chemotherapy, later Div. of Cancer Treatment, before he retired from government service to accept the Florida position.

NCAB TO CONSIDER FATE OF SOME EXISTING, 2 POSSIBLE NEW COMPREHENSIVE CENTERS

The May30-31 meeting of the National Cancer Advisory Board may be one of the most important since the Board was created by the National Cancer Act of 1971. Items on the agenda include:

- The report of the Subcommittee on Centers and the Board review of existing comprehensive cancer centers. The review was initiated two years ago to determine how well the centers are doing their job, how well they are meeting the 10 characteristics of comprehensive centers as determined by the Board, and possibly to consider the question of removing those centers from the comprehensive list that do not meet the requirements and show evidence that they never will.
- The Subcommittee on Centers also will review prior to its report to the Board the requests for comprehensive recognition from the Michigan Cancer Foundation and the Missouri Cancer Programs. The subcommittee's recommendations may go to the Board at this meeting.
- Further consideration of the particle therapy proposals submitted by the Committee for Radiation Oncology.
- Full scale review of the Div. of Cancer Control & Rehabilitation.
- Adoption of NCI's opening round of budget requests for the 1980 fiscal year, and further consideration of distributions to be made with 1979 appropriations.
- A big list of new and renewal grant recommendations from the study sections, including some for cancer centers (to be considered in closed session).

Board subcommittees will meet in the morning May 30, with the first open Board session scheduled to start at 1 p.m. The Subcommittees on Planning & Budget and on Environmental Carcinogenesis will meet at 7:30 p.m., the latter to consider the status of environmental carcinogenesis studies supported by NCI.

Other items on the agenda include reports on research in oncopathology, upgrading animal research facilities, and reports from the NCI director and President's Cancer Panel.

This also could be the first meeting for the new chairman of the Board, and for a half dozen other Board members, if President Carter ever gets around to appointing them. If not, then Jonathan Rhoads, the only chairman the NCAB has ever had, may continue in that role if he so chooses. The Cancer Act says that Board members will served their appointed terms and may continue until they are replaced.

ADVISORY GROUP, OTHER CANCER MEETINGS FOR MAY AND JUNE

Governance and Structure of Cancer Centers—May 1-2, Los Angeles, sponsored by American Assn. of Cancer Institutes and NCI.

Cancer Control & Rehabilitation Advisory Committee—May 2-3, NIH Bldg 31 Room 10, 9 a.m., both days, open.

Developmental Therapeutics Committee— May 4, Blair Room 110, open 9–9:30 a.m.

President's Cancer Panel— May 9, NIH Bldg 31 Room 7, 9:30 a.m., open.

Cancer Research Manpower Review Committee Subcommittee on Cancer Etiology & Prevention—May 10-11, NIH Bldg 31 Room 8, closed.

Manpower Review Committee Subcommittee on Detection & Diagnosis, Treatment & Restorative Care—May 10-11, NIH Bldg 31 Room 8, closed.

World Conference on Lung Cancer—May 10-13, Hilton Head Island, S.C.

The Blood Platelet in Transfusion Therapy—May 10-11, Washington D.C. Pan American Health Organization, American Red Cross symposium.

Carcinogenesis Program Scientific Review Committee—May 11-12, NIH Bldg 31 Room 9, open 8:30–9 a.m.

Adolescent Oncology— May 11, Roswell Park continuing education in oncology, contact Claudia Lee.

Cancer Biology & Diagnosis Board of Scientific Counselors— May 12-13, NIH Bldg 31 Room 10, open May 12, 9 a.m.–5 p.m.

Cancer Research Manpower Review Committee—May 12, NIH Bldg 31 Room 7, open 9–9:30 a.m.

Clearinghouse on Environmental Carcinogens Plenary Session— May 15, NIH Bldg 31 Room 6, 8:30 a.m., open.

Committee on Cancer Immunobiology— May 15-17, Landow Room C418, open May 15, 7 p.m.–7:30 p.m.

National Cancer Advisory Board Subcommittee on Centers— May 16-17, NIH Bldg 31 Room 6, 8:30 a.m. each day, open.

Cancer Solutions Within Our Grasp—May 16, Marie Curie Memorial Foundation, London; miscellaneous advances in prevention & therapy of cancer.

Committee on Cancer Immunodiagnosis—May 21-23, Landow Room C418, open May 21, 7 p.m.–7:30 p.m.

Symposium on Environmental Carcinogenesis— May 21-23, Michigan State Univ. Cancer Center.

Combined Modality Committee—May 24, NIH Bldg 31 Room 9, open 8:30–9 a.m.

Breast Cancer Task Force—May 24-26, NIH Bldg 1 Wilson Hall, open May 24, 8:30 a.m.–adjournment.

International Symposium on Advanced Cancer Pain—May 24-27, Venice.

National Cancer Advisory Board—May 30-31, NIH Bldg 31 Room 6, open May 30, 1 p.m.—5 p.m.; May 31, 1 p.m.—adjournment.

NCAB Subcommittee on Centers—May 30, NIH Bldg 31 Room 8A30, open 8:30—9:15 a.m.

NCAB Subcommittee on Construction— May 30, NIH Bldg 31 Room 8A30, closed.

NCAB Subcommittee on Planning & Budget—May 30, NIH Bldg 31 Room 9, 7:30 p.m., open.

NCAB Subcommittee on Environmental Carcinogenesis— May 30, NIH Bldg 31 Room 6, 7:30 p.m., open.

World Congress on Diseases of the Chest—June 1-5, Kyoto.

Cancer & Nutrition Scientific Review Committee—June 1-2, Federal Bldg, 7550 Wisconsin Ave., Bethesda, Room 6C01, open 8:30—9 a.m. both days.

Large Bowel Cancer Review Subcommittee—June 1-2, Houston Anderson Mayflower, open June 1, 7:30 p.m.—8 p.m.

Biometry & Epidemiology Review Committee—June 1-2, Landow Room A809, open June 1, 7 p.m.—10:30 p.m.

Cancer Control Prevention, Detection & Pretreatment Evaluation Review Committee—June 1-2, NIH Bldg 31 Room 4, open June 1, 8:30 a.m.—5 p.m., June 2, 8:30 a.m.—noon.

Third National Training Conference for Physicians on Psychosocial Care of the Dying Patient—June 3-4, San Francisco, Univ. of California Cancer Research Institute.

In Situ Expressions of Anti Tumor Immunity—June 407, Tel Aviv.

World Conference of Gastroenterology—June 5-9, Madrid.

Developmental Therapeutics Committee— June 8, NIH Bldg 31 Room 7, open 9 a.m.—adjournment.

Bladder Cancer Review Subcommittee— June 8, Chicago O'Hare Hilton, open 8:30—11 a.m.

Present Status of Management of Prostatic & Bladder Cancer with Emphasis on Radiotherapy—June 9, Roswell Park continuing education in oncology.

DES Task Force—June 9, NIH Stone House, Room 16A, open 9:30 a.m.—adjournment.

President's Cancer Panel—June 12, NIH Bldg 31 Room 7, 9:30 a.m., open.

Cancer Special Programs Advisory Committee— June 12-13, NIH Bldg 31 Room 4, open 9—10:30 a.m.

Committee on Cancer Immunotherapy Subcommittee on Cause & Prevention—June 12-13, NIH Bldg 10 Room 4B14, open 1:30-2 p.m.

Cancer Control Grant Review Committee—

Management of Colorectal Cancer—June 15-16, Wilmington, Dela., Hotel duPont, regional nurse conference sponsored by Delaware Cancer Network.

Committee on Cancer Immunotherapy— June 15, NIH Bldg 10 Room 4B14, open 1:30—2 p.m.

Cooperative Group Chairmen— June 20, NIH Bldg 31 Room 9, 11 a.m., open.

Committee on Cancer Immunobiology— June 20, NIH Bldg 10 Room 4B14, open 2—2:30 p.m.

Virus Cancer Program Scientific Review Committee— June 22-23, Landow Room 9B04, open June 22, 9—9:30 a.m.

EORTC Symposium on Adjuvant Therapy & Biological Markers of Cancer—June 22-24, Centre Nationale de la Recherche Scientifique, Paris.

Prostatic Cancer Review Subcommittee— June 23, Roswell Park Memorial Institute, Buffalo, open 8:30—9 a.m.

Cancer Control Community Activities Review Committee—June 23, Blair Room 110, open 8:30—9 a.m.

Cancer Clinical Investigation Review Committee—June 26-27, NIH Bldg 31 Room 6, open June 26 9 a.m.—noon.

Clearinghouse on Environmental Carcinogens Chemical Selection Subgroup—June 27, NIH Bldg 31 Room 7, 8:30 a.m., open.

Clearinghouse Experimental Design Subgroup—June 28, NIH Bldg 31 Room 7, 8:30 a.m., open.

Cancer Control Treatment, Rehabilitation & Continuing Care Review Committee—June 29, NIH Bldg 31 Room 10, open 8:30 a.m.—3 p.m.

Clearinghouse Data Evaluation/Risk Assessment Subgroup— June 29, NIH Bldg 31 Room 7, 8:30 a.m., open.

Committee on Cytology Automation—June 29, NIH Bldg 10 Room 1A21, open 1:30 p.m.—adjournment.

Carcinogenesis Program Scientific Review Committee— June 29-30, Landow Room C841, open June 29, 8:30—9 a.m.

National Conference on Nutrition in Cancer—June 29-July 1, Washington Plaza Hotel, Seattle, sponsored by ACS & NCI. Contact S.L. Arje, ACS, 777 Third Ave., New York 10017 or ACS divisions.

International Endocurietherapy Symposium—June 30-July 2, Univ. of Southern California. Contact Frederick George, USC, 2025 Zonal Ave., Los Angeles 90033.

ABSTRACTS OF SELECTED PAPERS PRESENTED AT ANNUAL AACR MEETING

Following are abstracts of papers presented at the 69th annual meeting of the American Assn. for Cancer Research. These papers were selected by the program committee as worthy of special attention. Others will appear next week in *The Cancer Letter.*

RADIOSENSITIVITY IN VITRO OF FIBROBLASTS FROM CANCER PATIENTS AND DONORS AT HIGH RISK OF CANCER

— Alvaro Macieira-Coelho, Catherine Dietloff, Bruno Azzarone, Edmond P. Malaise and Daniel Fries, Institute de Cancerologie et Immunogenetique (INSERM U50) et Institute de Radiobiologie Clinique, Villejuif, France

When fibroblasts from different species were tested concerning their sensitivity to low dose rate ionizing radiation, it was found that establishment was accelerated in those fibroblast populations (Nature 261, 1976, 586) that yield spontaneously permanent cell lines. The same experiments were made with human fibroblasts to see if there would be a different response between cells from normal donors and at high risk of cancer, and from neoplastic patients. The cells were irradiated with 100 rads (0.27 rads.min.$^{-1}$) 1,2,3,4 and 5 times and were counted in each group at each passage until the end of their lifespans in vitro.

Under our experimental conditions, the lifespan of irradiated human embryonic fibroblasts was identical to that of the controls. Irradiation shortened the lifespan of normal human adult fibroblasts. However, human adult fibroblasts derived from cancer patients had survival curves identical to those of embryonic cells. In fibroblasts from some donors at high risk of developing neoplasias, the division potential was stimulated by low dose rate ionizing radiation. The data support previous results suggesting changes in vitro of fibroblast-like cells from patients with or prone to neoplasia and are of potential value for attempts to distinguish between donors genetically prone to cancer.

PROMOTING EFFECT OF DL-TRYPTOPHAN AND SACCHARIN IN URINARY BLADDER CARCINOGENESIS IN THE RAT

— S.M. Cohen, M. Arai and G.H. Friedell, St. Vincent Hospital, Worcester, Mass.

The effect of feeding DL-tryptophan (2% of diet) or saccharin (5%) to male weanling Fischer rats alone or after 6 weeks of 0.2% N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT), was evaluated over a 2 year experimental period. Bladder papilloma developed in none and carcinoma in 3 of 19 rats fed 6 weeks of FANFT followed by control diet, and 20 of 20 rats fed FANFT for 36 weeks followed by control diet developed carcinoma. FANFT for 6 weeks followed immediately by DL-tryptophan resulted in papilloma in one and carcinoma in 9 of 19 rats whereas papilloma developed in 7 and carcinoma in 7 of 20 rats fed DL-tryptophan after 6 weeks of FANFT and 6 weeks of control diet. Saccharin after 6 weeks of FANFT induced papilloma in one

and carcinoma in 17 of 19 rats, and saccharin fed after 6 weeks of FANFT plus 6 weeks of control diet resulted in papilloma in 4 and carcinoma in 9 of 18 rats. Most of the rats fed tryptophan survived to the end of the experiment (104 weeks), whereas rats administered saccharin after FANFT, or after FANFT and control diet, had decreased survival usually due to hematuria secondary to tumor formation with average survival of 93 and 96 weeks, respectively. No bladder tumors were observed in 18 rats administered only tryptophan, 20 rats fed saccharin, or 40 rats fed control diet only. Mild bladder hyperplasia was observed in rats at the end of the 6th week of FANFT, but regressed to normal after 6 weeks of control diet.

DL-tryptophan and saccharin enhanced bladder carcinogenesis when administered immediately after 6 weeks of FANFT or after 6 weeks of FANFT plus 6 weeks of control diet.

SACCHARIN AND CYCLAMATE IN HUMAN BLADDER CANCER — Irving Kessler and J. Page Clark, Johns Hopkins

An epidemiologic study was undertaken to investigate the roles, if any, of artificial sweeteners in human bladder cancer. 519 patients with histopathologically confirmed urinary bladder cancer and an equal number of demographically similar controls without bladder disease were subjected to intensive interview regarding their dietary intake of cyclamate- and saccharin-containing food and drink. Smoking habit, occupation, age, diabetes mellitus, diet and other potentially confounding factors were considered in the analysis. The relative risk of bladder cancer was not significantly increased by saccharin or cyclamate use and no relationship of cancer risk with sweetener dose or duration was evident. It is concluded that neither saccharin nor cyclamate in physiologic doses is carcinogenic to the human bladder.

INDUCTION OF COMPLETE REMISSION FROM DISSEMINATED OAT CELL CARCINOMA BY INTENSIVE CHEMORADIOTHERAPY AND BONE MARROW AUTOTRANSPLANTATION — Peter Graze, Winston Ho, John Wells, and Martin Cline, UCLA

Bone marrow suppression is frequently a limiting factor in cancer treatment. Rescue from otherwise life threatening pancytopenia by reinfusing hematopoietic stem cells previously obtained and cryopreserved may permit intensive treatment of sensitive tumors refractory to conventional therapy. Bone marrow was obtained from a 39 year old male with oat cell carcinoma limited to thorax at presentation. Following marrow cryopreservation, he received multi-agent chemotherapy including cyclophosphamide, methotrexate, adriamycin, vincristine, CCNU, and procarbazine. Despite this regimen, disease progression occurred, and five months later metastases were documented in lung, lymph nodes, bone, brain, liver, and bone marrow. Treatment then included fractionated radiation to brain, liver, and lung, and chemotherapy with methotrexate (200mg/kg), citrovorum factor, adriamycin (150mg/m^2), cyclophosphamide (120mg/kg) and total body irradiation (800Rad). Cryopreserved bone marrow containing $1.4x10^6$ CFU-C was re-infused 60 hours after completion of therapy. By 4 weeks, repeat studies demonstrated complete resolution of all documented areas of disease. Return of bone marrow hematopoiesis was documented by day 14, and the patient was discharged from the hospital on day 28 in complete remission. Toxicity included transient pancytopenia and stomatitis. This experience demonstrates that the developing apparent resistance of oat cell tumors to conventional therapy may be a dose-related phenomenon. Furthermore, autografting of cyropreserved bone marrow cells can provide practical adequate protection from the otherwise intolerable hematologic toxicity of intensive combined modality treatment.

Our experience suggests that this approach may provide effective treatment for a variety of disseminated malignancies.

CORRELATION OF CELLULAR AND MOLECULAR REPAIR PROCESS IN XERODERMA PIGMENTOSA (XP) AND ATAXIA TELANGIECTASIA (AT) FIBROBLASTS: A POSSIBLE EXPLANATION FOR THE HIGH TUMOR INCIDENCE IN THESE PATIENTS — Ralph Weichselbaum, Joint Center for Radiation Therapy, Harvard Medical School, and John Little, Harvard School of Public Health

XP is an autosomal recessive disease characterized by the development of multiple malignant skin tumors. Fibroblasts from these patients show a deficiency in the repair of UV induced DNA damage. AT is an autosomal recessive disease characterized by the predisposition of malignant tumors. Fibroblasts from these patients are sensitive to killing by gamma irradiation and a defect of gamma induced DNA repair has been demonstrated in cells from some of these patients. Survival enhancement after a delay of subculture and density inhibited (slowly proliferating) cultures has been termed potentially damage repair (PLDR). We have demonstrated deficiencies in x-ray PLDR in AT cells. These findings suggest PLDR as a general phenomenon in density inhibited cells may reflect molecular repair processes, and that independent repair pathways exist for x-ray and UV. If malignancies arise in stem cells in a quiescent phase of growth, and if DNA damage may be repaired in such cells by mechanisms which act particularly efficiently in non-proliferating cells, then these deficiencies in PLDR might explain the high incidence of malignancies in these patients.

TRANSFORMATION OF HUMAN NEUROBLASTOMA CELLS INTO GANGLION CELLS IN VITRO WITH MITOMYCIN-C — Milton Goldstein, Washington Univ. School of Medicine

We have previously shown that human neuroblastoma cells of primary cultures and of established lines are stimulated by a protein, Nerve Growth Factor (NGF) to increase in size, and show accelerated neurite outgrowth, and an increase in proteins specific to sympathetic neurons. Although many tumor cells differentiated, relatively few became nondividing ganglion cells, especially among the cells of established lines.

To determine if inhibition of growth would stimulate differentiation, cells of three established lines of human neuroblastoma were exposed to a number of drugs which inhibited cell multiplication including mitomycin-C. Only mitomycin-C caused a gradual mass transformation of small immature neuroblastoma cells into large nondividing ganglion cells. Cells were pulsed for one hour at 37°C with 4 to 5 γ/-ml of the drug. Depending on the cell line, 40% to 75% of the cells survived and these were transformed over the following 2 weeks into aggregates of nondividing ganglion cells with very large multipolar neurites. Eventually the aggregates of cell bodies and neurites covered the entire surface of the flasks in which they were grown. The mitomycin-C treated tumor cells were very sensitive to stimulation by NGF. Although NGF was not required for transformation, mitomycin-C treated cells grown with NGF had more survivors, produced a more dense outgrowth of neurites and collateral fibers and now require NGF to survive for many months in vitro. The transformation of neuroblastoma cells into ganglion cells in vitro provides a model for the study of this phenomenon which occurs in some children with neuroblastomas after treatment with alkylating agents.

NUCLEAR GLUCOCORTICOID BINDING IN CHRONIC LYMPHATIC LEUKEMIA (ALL) — John Stevens, Yee-Wan Stevens, Jonathan Rhodes, Esther Sloan and Robert Rosenthal, Hospital for Joint Diseases, Mount Sinai School of Medicine

Under specific circumstances, glucocorticoid administration may be the treatment of choice for CLL. However, the mechanism of response to steroid therapy is unknown. Since corticoids may act via glucocorticoid receptor (GR) binding to chromatin, we investigated whether CLL lymphocytes contain nuclear GR. 2M sucrose-Triton X 100 purified nuclei, isolated from peripheral CLL cells which had previously been incubated (60 min, 37°) with ^{3}H-triamcinolone acetonide (^{3}H-TA), were extracted with 0.6M KCl at 4°. Presence of the protease inhibitor CBZ-L-Phe during KCl extraction was essential for obtaining high levels of bound ^{3}H-TA (52-65% of extracted cpm) in the KCl extract. Omission of CBZ-L-Phe resulted in only 12% macromolecular-associated ^{3}H-TA. CBZ-L-Gly was ineffective.

In contrast, $MgCl_2$ and spermidine in dilute buffer caused a concentration dependent release of bound (52-69%) nuclear ^{3}H-TA in the absence of KCl or CBZ-L-Phe with maximal effects at 4mM and 5mM respectively. These results suggest GR association with CLL nuclei may depend on charge interactions. 2M sucrose completely prevented the Mg-induced release of nuclear ^{3}H-TA. Nuclear ^{3}H-TA binding under intact cell conditions was maximal at 10nM ^{3}H-TA, of limited capa-

city (3100 molec. bound ^{3}H-TA/nucleus) and competable by active glucocorticoid binding and its role in steroid action in primary human lymphoproliferative disease.

NUCLEAR MIXED FUNCTION OXIDASE (MFO) ACTIVITY: ITS ONTOGENY AND IMMUNOLOGY – Edward Bresnick, J.C. Nunnink, A.H.L. Chung, B. Hassuk, B. Boraker, Univ. of Vermont College of Medicine and Vermont Regional Cancer Center, and W. Levin and P.E. Thomas, Hoffmann-LaRoche

Previous work from this laboratory has indicated the presence of aryl hydrocarbon hydroxylase (AHH) and cytochrome P_{450} (cyt P_{450}) within nuclei (nuc). The aims of the present study were to a) examine the ontogeny of nuc AHH, b) establish the immunological relatedness of microsomal to nuc cyt P_{448} and c) to look for other nuc MFO activities. Nuc AHH was present in the 18-20 day fetal rat liver at a low level (5pg/min/mg) and rose rapidly post-partum. The liver nuc AHH activity in 6g, 20g and adult rats was 173, 575 and 1191, resp. Nuc AHH was markedly inducible by 3-methylcholanthrene (MC), with the newborn rat being the most responsive (elevated by 29 fold). Induced nuc activity was also seen in fetal liver after MC administration to the dam. Antibody to microsomal cyt P_{448} cross-reacted with nuc cyt P_{448} exhibiting a zone of identity. Further proof of the localization of cyt P_{448} within nuc was obtained by incubating anti-cyt P_{448} (prepared in rabbits to the microsomal hemoprotein) with cross-sections of nuc embedded in agar, washing off the unfixed antibody, incubation with anti-antibody (prepared in goats) to which β-galactosidase was coupled and then measurement of β-galactosidase activity by

SUPPRESSION OF MALIGNANCY IN INTRASPECIFIC HUMAN CELL HYBRIDS: THE GENERALITY OF THE PHENOMENON – Bernard Weissman and Eric Stanbridge, Univ. of California (Irvine)

Recently we have reported that malignancy is suppressed in human-human cell hybrids derived from fusions between HeLa and a variety of normal human fibroblasts. In order to establish the generality of this phenomenon, we have isolated hybrids between different malignant human cell lines and a variety of normal human cells. The tumor cell lines used cover a broad spectrum of tumor types, including carcinomas, sarcomas, and lymphomas. Selection of hybrids was carried out by using a selective procedure where one parent cell is ouabain-resistant and hypoxanthine-guanine phosphoribosyl transferase-dificient and the other parent cell is wild type. Selection is accomplished in HAT medium containing 5×10^{-7} M ouabain. The tumorigenicity of the hybrid lines was assayed in nude athymic mice. Our preliminary evidence indicates that the suppression of malignancy is a general phenomenon. Furthermore, in each of these hybrids it appears that malignant and transformed phenotypes (characterized by in vitro properties such as anchorage independence, lectin agglutination, etc.) are under separate genetic controls. The significance of the apparent recessive nature of the malignant phenotype and the dominant or codominant expression of the transformed phenotype will be discussed.

SOME BIOCHEMICAL EFFECTS OF ANGUIDIN IN VIVO – Bonnie Bowdon, Jacqueline Werline and Glynn Wheeler, Southern Research Institute

Anguidin, which is produced by several soil fungi, is of current interest because it is active against several experimental neoplasms. Other investigators studied the biochemical effects of this agent upon cultured cells and in cell-free systems and concluded that it primarily inhibits the initiation of protein synthesis and secondarily inhibits synthesis of DNA and RNA. We have extended these studies to mice bearing leukemia L1210, colon tumor 26, colon tumor 36, or colon tumor 38 and have compared the effects upon macromolecular synthesis by marrow, spleen, colonic mucosa, and the cancers. A single i.v. dose of anguidin caused extensive transient inhibition of synthesis of protein, DNA and RNA by all of the tissues examined, but the rates of recovery differed for the various tissues. Synthesis of DNA was inhibited as much as, or more than, synthesis of protein; synthesis of RNA was inhibited less than that of protein. Recovery of synthesis of protein and of RNA preceded recovery of DNA synthesis in several instances. Anguidin caused early increases in the pools of ribonucleotides followed by decreases to subnormal levels in colon and tumor 38, and the decreases were greater in the tumor. In vivo treatment with anguidin caused a transient decrease in the DNA polymerase activity of L1210 cells followed by an increase to levels exceeding that of the control, but the addition of anguidin to a cell-free preparation from untreated L1210 cells did not alter the DNA polymerase activity.

Thus, inhibition of protein synthesis might result in decreased activities of enzymes required for the synthesis of nucleic acid. Specific knowledge about such decreases might be useful in planning combination therapy utilizing anguidin with other agents.

THE ARYL HYDROCARBON HYDROXYLASE POLYMORPHISM AND RESPIRATORY CANCER – Beverly Paigen, E. Ward, Hira Gurtoo, Jun Minowada, Ronald Vincent, Natalie Parker and Kenneth Paigen, Roswell Park

This study was designed to test whether the aryl hydrocarbon hydroxylase (AHH) polymorphism in humans affected susceptibility to lung and laryngeal cancer. It was previously reported by others that lung and laryngeal cancer patients were in the high end of the AHH inducibility range indicating a genetic susceptibility to respiratory cancer. Previously we reported that it was difficult to measure AHH inducibility in about half of lung cancer patients due to a failure of their lymphocytes to grow, respond to mitogens, and synthesize AHH normally during cell culture. An indirect assessment of the distribution of AHH inducibility in lung cancer patients, determined by testing the progeny of lung cancer patients, showed no difference between the progeny and the matched control. We now report a study of persons who had lung or laryngeal cancer but who had the cancer removed by surgery. At the time of testing, these former patients were no longer ill and their lymphocytes responded normally during culture. A comparison of AHH inducibility in these former patients compared with a match set of controls showed no difference in AHH inducibility between the two populations. These data indicate that the genetic polymorphism of AHH inducibility does not predispose to respiratory cancer.

INCREASED ABUNDANCE OF SPECIFIC mRNA AND CYTOSOL PROTEINS IN RAPIDLY GROWING TUMORS – Harris Busch, Friedrich Hirsch, Harold Morris, Katrina Nall, Katari Raju, S. Ann Johnson, William Spohn and Hiroshi Takami, Baylor College of Medicine

Total polysomal poly (A)+ RNA of Novikoff hepatoma (NH) and of 18-hour regenerating rat liver (RRL) were compared by analysis of their in vitro translational products on 2D isolfocusing/SDS gels. The translated proteins resolved sufficiently to discriminate differences between these mRNA populations. Excess cDNA from RRL or NH covalently linked to cellulose was used to adsorb the complementary mRNA sequences from NH or RRL. As shown by 2D gels, translated products of the bound mRNA fractions contained many proteins common to both tissues. NH mRNA which did not bind to cDNA was enriched in sequences coding for proteins (MW/pI) 12.5/4.9, 13.5/7.4, 17/8.2, 24/5.5 and 46/6.4 which were not found in the translational pattern from NH mRNA. Thus, adsorption of mRNA to solid phase cDNA is valuable for differentiating mRNA species and identification of their products in related tissues as well as for enrichment of specific mRNAs. Abundant cytosol proteins of rat liver, Morris hepatoma 9618A, 8999, 3924A, Novikoff hepatoma and normal rat tissues were then separated by 2D gels. An increasing number of proteins absent from liver were found with increased growth rate of the tumors, e.g. proteins (MW/pI 24.5/7.2 and 79/6.7. The marked variation in proteins detected in the rapidly growing Novikoff and 3924A hepatomas supports the concept of dysplastic protein synthesis in tumor cells.

INTERCALATOR-INDUCED PROTEIN-ASSOCIATED DNA STRAND BREAKS IN MAMMALIAN CELLS – Warren Ross, Daniel Glaubiger and Kurt Kohn, NCI

Adriamycin and other intercalating agents have been reported to produce DNA single-strand breaks in mammalian cells. To investigate the nature of these breaks, we used the method of alkaline elution to study the effects of adriamycin and ellipticine on DNA in L1210 cells. Direct assay by this method failed to reveal drug-induced strand breaks.

Since strand breaks can be concealed by DNA-protein crosslinks in alkaline elution assays (R.A.G. Ewig and K.W. Kohn, Cancer Res. 37: 2114 '77), proteinase-K was used to remove any such crosslinks. These assays showed that drug treatment produced both DNA-protein crosslinks and DNA strand breaks, but that the breaks were completely concealed by protein. By contrast, the drug-induced DNA-protein links only partially concealed an equal frequency of x-ray induced strand breaks, suggesting spatial proximity between the drug-induced strand breaks and protein links.

Using a recently developed method to quantitate DNA-protein links (Ewig & Kohn, in preparation), the frequencies of drug-induced protein-links and strand breaks were found to be within a factor of 2 of each other. Protein-associated strand breaks were also produced by the intercalators, ethidium and actinomycin, but not by the non-intercalating DNA-binder, anthramycin. Since ellipticine and ethidium contain no quinone moieties, a previously suspected mechanism of DNA breakage via quinone-induced free radicals is excluded in this case. Our findings suggest DNA single-strand breaks that have covalently linked protein at the break sites. This is known to occur in the case of DNA relaxase.

The protein-associated breaks thus may represent a cellular response to the helix distortion that results from intercalation.

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, citing the RFP number. Some listings will show the phone number of the Contract Specialist, who will respond to questions Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Their addresses, all followed by NIH, Bethesda, Md. 20014, are:
Biology & Diagnosis Section — Landow Building
Viral Oncology & Field Studies Section — Landow Building
Control & Rehabilitation Section — Blair Building
Carcinogenesis Section — Blair Building
Treatment Section — Blair Building
Office of the Director Section — Blair Building
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CP-VO-81040-60

Title: *Retroviral expression during primate carcinogenesis*
Deadline: *June 23*

NCI will make available to interested contractors a request for proposal for studying retroviral expression during primate carcinogenesis. This project will focus on the utilization of primate cell model systems to determine cellular control of integration and expression of these sequences and on identification and characterization of retrovirus-related molecules in human tissues.

Specific experience in the following areas is required: (1) Purification and characterization of probes for retroviral information in cells; (2) in vitro culture of primate tissues; characterization of cell cultures; (3) nucleic acid hybridization assays; (4) reverse transcriptase assays; (5) protein purification and characterization; (6) detection of integrated proviral genomes in cellular genome; (7) detection of viral mRNA in cells; (8) detection of retrovirus proteins in cells; and (9) systems for detection of cellular control of virogene expression.

Contracting Officer: Charles Fafard
Viral Oncology & Field Studies
301-496-1781

RFP NO1-CP-85626-72

Title: *Procurement of metabolic samples for the assessment of the role of diet and nutrition on the production of mutagenic/carcinogenic substances in humans*
Deadline: *June 16*

The primary objective of this project is to obtain an adequate number of biological samples such as urine, feces, saliva, blood, breast milk, etc. from defined and controlled metabolic studies to conduct in vitro mutagenicity or carcinogenicity studies.

The offerors should discuss the types and number of samples available. The specific circumstances under which they were collected and stored, and procedures for shipment. The samples may come from past, ongoing, or future studies. All samples will be shipped by September, 1980 to a central repository for subsequent distribution. It is anticipated that this project will involve a two year period of performance including shipping and documentation of all samples.

Contractors must agree to make available all collected information and data relative to the study for which the samples were collected initially, including documentation of dietary intake, collection procedures, subject profiles, and any analyses conducted on the samples.

Contract Specialist: Jackie Matthews
Carcinogenesis
301-427-7574

CONTRACT AWARDS

Title: Breast Cancer Detection Demonstration Project, renewal
Contractor: Samuel Merritt Hospital, Oakland, Calif., $252,152.

Title: Evaluation of pharmacologic agents for the treatment of anorexia in the cancer patient
Contractor: Instituto di Richerche Farmacologiche "Mario Negri," Milan, $192,456.

Title: Cervical Cancer Screening Program, renewal
Contractor: Alabama Dept of Health, $92,302.

The Cancer Letter —*Editor* JERRY D. BOYD

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