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AACR, ASCO MEMBERS CONCERNED OVER ETHICS, SOCIAL ISSUES, AND WHAT TO DO ABOUT THEM

Ethics and social issues involved in cancer research and in the care of cancer patients turned out to be the dominant theme of the joint annual meeting of the American Assn. for Cancer Research and the American Society of Clinical Oncology last week in San Diego.

Members overflowed the meeting room for a seminar on "Social and Ethical Issues in Cancer Prevention and Therapy," chaired by Michael Brennan, Michael Shimkin and Gordon Zubrod. The spirited exchange between panelists and the audience left little doubt that oncologists and scientists are keenly aware of ethical and social problems they are facing and are greatly concerned about how to resolve them.

Van Rensselaer Potter, retiring AACR president, expounded on the subject in his address, "Humility with Responsibility: A Bioethic for Oncologists."

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In Brief

NCI MAY SUPPORT STUDIES OF HEAT AS THERAPEUTIC METHOD; DTIC OK NEAR FOR MALIGNANT MELANOMA

HEAT as a potential cancer therapeutic modality is under review for possible NCI support. Vincent DeVita, director of the Div. of Cancer Treatment, said studies that show cancer cells start to disintegrate at increasing temperatures before normal cells do "suggest we should get involved in developing heat technology." Diathermy, microwave mechanisms could be used. . . . **JOHN LANE**, executive secretary for the Cancer Clinical Investigation Review Committee, will leave that position at the end of May to take the same job with the Cancer Control Grant Review Committee. . . . **RAUL MERCADO** is the new chief of the Clinical Investigations Branch in NCI's Div. of Research Resources & Centers. He moved over from the Div. of Cancer Control & Rehabilitation. . . . **AWARDS:** To NCI Director Frank Rauscher, the HEW Distinguished Service Award for "outstanding leadership and committment to the National Cancer Program" and for the discovery of the Rauscher leukemia virus; and to George Todaro, chief of NCI's Viral Leukemia & Lymphoma Branch, the $1,000 American Society for Experimental Pathology award to the "member under 40 years of age who has made the most outstanding contribution to the conquest of disease" in the past year. . . . **NEW ANTICANCER** drug, DTIC, will soon be approved by FDA for use against advanced, wide-spread malignant melanoma. DTIC (dacarbazine, DIC, or imidazole carboxamide), was developed by NCI, first synthesized by Y. Fulmer Shealy and colleagues at Southern Research Institute, and will be marketed by Miles Labs. Clinical studies resulted in a 22% response rate, with average length of response at four months, although some are free of disease three years after DTIC therapy.

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SHOULD PUBLIC BE TOLD OF POSSIBLE CARCINOGEN? TIMING IS ETHICAL ISSUE

(Continued from page 1)

"What actions should be taken by the membership of the American Assn. for Cancer Research to influence national policy in matters involving cancer prevention?" Potter asked. "The answers involve bioethics. Thas is, they require the possession of biological knowledge plus value judgments as to the priority of the various competing policy decisions."

Potter suggested that bioethics is a "new discipline that combines biological knowledge with a knowledge of human value systems in an open-ended biocybernetic system of self-assessment."

Artificial prolongation of life without meaning, death with dignity, and human experimentation are questions that must be considered by those in clinical oncology, Potter acknowledged. "However, my own view of bioethics calls for a much broader vision . . . A wider and more purposeful understanding of biological evolution and cultural evolution. . . And the development of environmental bioethics, a matter of major concern to oncologists."

Potter emphasized that "medical bioethics is only one fact of the problem of integrating biological knowledge with human value systems. The other facet is environmental bioethics. . . . . Oncologists are affected in every part of this formulation. In medical bioethics, the testing of new drugs and the wisdom of 'when to do and when to let be' are problems that confront the cancer therapist constantly.

"On a broader front, environmental ethics confronts the oncologist concerned with cancer prevention. An issue in cancer prevention is concerned with the opposing considerations of time and certainty. When human activity—a pollutant or a process or a cultural practice—is suspected of causing cancer, the first indications will come long before certainty and hard statistical estimates of risk are available. There is always the risk of crying 'wolf wolf' when there is no wolf, and there is the danger of waiting until hundreds or thousands of people have been placed at risk . . . . The question arises, is it ethical to withhold the first indications, or, putting it another way, under what circumstances is it ethical to withhold the first indications?"

Potter suggested that AACR "could do more than we are" about cigarette smoking: Go on record opposing the encouragement of the use of the use of agricultural lands for tobacco growing, and encourage members to participate in antismoking education programs.

Potter said he developed the idea of "humility with responsibility as the basic bioethic" out of consideration of what he called the "three properties of the Eureka! feeling—suddenness, euphoria, and fallibility. . . . The ethical imperative of the Eureka! feeling is to consider the possibility of error and look for a way to test the idea. . . . The ethic of humility with responsibility is nowhere more appropriate than in the life of the oncologist, because so many disciplines come to bear on the problem of cancer."

Seminar panelists tackled specific ethical problems. Umberto Saffiotti, who heads NCI's carcinogenesis program, pointed out that a time lag of up to a year can exist between the first clear awareness of the carcinogenic effect of a substance and the termination of the test period, followed by more time required for analysis, pathology, and final review.

"A delicate ethical dilemma confronts us in selecting the proper timing and extent for the release of carcinogenesis test results," Saffiotti said. "Early findings may not be confirmed by definitive evidence and their premature release may cause technological and economic problems as well as unnecessary anxiety. On the other hand, delaying public notification of highly suspicious preliminary findings until a final detailed report on the bioassay is compiled and reviewed may delay preventive actions for the protection of the exposed population from unnecessary risks. Quality judgment on the evidence of an early finding is critical in deciding on the likelihood that it be subsequently confirmed. . .

"Considerable consensus is developing on the appropriateness of public disclosure of early findings of a carcinogenic response," Saffiotti continued. "We share this point of view, provided that preliminary findings be clearly identified as such in a context which defines the conditions of test and the nature of the preliminary evidence and then only when the preliminary evidence is such that it suggests a good likelihood the positive findings will be confirmed."

Saffiotti said NCI has initiated a procedure for for issuing a "memorandum of alert" through HEW's Committee to Coordinate Toxicology and Related Programs. The memorandum will include a clear statement of the provisional nature of the reports.

"Only the definitive conclusive evidence should evoke regulatory or legal consequences," Saffiotti said. "The time between the alert and the definitive publication of the evidence hopefully should be understood by all concerned to be a time for preparing the appropriate response and plan of action for the case and time in which the carcinogenic activity of the test substance receives definitive confirmation."

Shimkin's comments included his assertions that:

- "We have no scientific base for carcinogenesis tests.
- "At the present time, all legislative and regulatory decisions (related to carcinogenesis) must be judgmental. We have panels of experts who are basically ignorant of what they are expert about.
- "People who generate data should not be the ones who interpret it. The concern that manufactures a product should not be the witness, judge and jury in evaluating its effect on the consumer."

J.H. Weisburger, New York, said that "something

has gone wrong in the communication of scientific data to the press." He cited as an example the "scare" headlines in both the lay press and scientific journals over the possibility that drinking water in some areas may contain some carcinogenic substances. There is no real data yet to support the contention that the public health is threatened, Weisburger said. Such "scares" lead the public into the feeling that "everything causes cancer so why worry about it," he said, causing them to ignore more dangerous health hazards such as cigarette smoking.

J.D. Scribner, Seattle, suggested that both EPA and FDA definitions of carcinogens are inadequate and inexact. A true carcinogen, he said, is one whose action is irreversible.

M.F. Cranmer, Jefferson, Ark., pointed out that suspected agents often cannot be eliminated by regulation or legislation. It is essential that research be undertaken to determine what levels threaten public health so that effective controls be undertaken, he said.

Zubrod said that oncologists frequently have the dual role of healer and experimenter which is a conflict of interest. In the past this was resolved in part "by the quality of the people doing research. No one questioned whether or not the research was for the benefit of the patient," Zubrod said. He suggested that medical schools should include considerations of character in their admission policies. "Sometimes the wrong people are admitted."

More complicated research now makes it necessary for the patient to have an advocate, Zubrod said. "Society can't afford two classes of citizens, one which can be used in research and one which can't."

M.J. Krant, Boston, asked these questions in discussing informed consent:

- "Can the physician be loyal to the patient and to research?
- "Do we educate young physicians on issues involved in experimentation?
- "If we ask patients to become experimentalists, do we ask them to volunteer?
- "Do we sometimes take short cuts in our efforts to participate in cancer research?
- "Do we always consider alternative treatment methods?"

Ethical issues involved in screening strategies were discussed by A.I. Sutnick—cost effectiveness, determination of which populations should be screened, possible risks to persons being screened.

Susan Sieber of NCI called attention to the possibility that some anticancer agents could be "double edged swords," in that they may cause second cancers in patients.

Sieber's studies show that Hodgkin's disease patients treated with vincristine, nitrogen mustard, chlorambucil, or with combination chemotherapy (nitrogen mustard, vincristine, procrabazine and prednisone) plus irradiation have a higher than normal incidence of acute myelogenous leukemia. The rates for AML are up to 100 times that of the general population among some groups of Hodgkin's disease patients, she said.

Some groups of multiple myeloma patients treated with L-PAM have shown an incidence of AML from 100 to 1,000 times that of the general population, Sieber reported.

Sieber acknowledged that acute leukemia may be part of the natural history of myeloma or Hodgkin's disease, a possibility that is only now becoming evident because of the increases in patient survival due to improved treatments.

QUALITY CARE REQUIRES CHANGING OLD REFERRAL PATTERNS, PANEL INSISTS

The major problem to be overcome in bringing optimal treatment to the cancer patient at the community level is the need to break up existing referral patterns.

Joseph Prorok, Allentown, Pa., who is active in developing a cancer program for that community, offered that conclusion to participants in a workshop, "Oncology in the Community," at the AACR/ASCO meeting.

The panel members agreed with moderator M.D. Prager's comment that "referrals are usually not based on the competence of the physician to whom the patient is referred." But members of the audience responded by suggesting that changing referral patterns is not easily done since it frequently involves personal and established professional relationships.

Panel member Robert Martin of Hartford, Conn., said that oncology nurses "can play a terrific role" in that regard. He cited his community's oncology nursing program, which includes a nurse oncologist on the hospital's coordinating committee and the training of visiting nurses.

"Nurses are capable of changing referral patterns by beating on the physicians," Martin said. "They'll take the initiative and tell you who is best for the patient."

Interestingly, the two specialists on the panel—surgeon Prorok and radiotherapist C.R. Koons of Boise—although assigned to discuss those single modalities in the community setting, emphasized the value of the team approach.

"The surgeon has to know what other modalities are available," Prorok said. "The community surgeon cannot be an oncological surgeon—it is something that is thrust upon us. There are not enough patients to develop the expertise of all the surgeons. So the major problem is to try to break down existing referral patterns. The multiplicity of surgeons within the community exacerbates the problem. The quality of care is erratic; equality of care inconsistent.

"The multidisciplinary approach must be guaranteed. That is the key to assuring patients of good

care at our level."

Prorok concluded his remarks with a quote from Tolstoy that may have shocked some of his fellow surgeons: "The real doctors are in the mountains," Tolstoy wrote. "They know about the herbs."

"That's who will be making the improvements in cancer treatment," Prorok said. "The herb doctors."

Koons stressed the value of the "team" approach. "Perhaps the future will show that it is more realistic to have the patient managed by an expert in the disease entity, who is also knowledgeable about the benefits and disadvantages of each therapeutic skill or technique, but not necessarily skilled himself in each," Koons said.

"The approach is through the biology of the disease and not through the mode of treatment. The successful oncologist of tomorrow will be much more knowledgeable of his colleague's skills. He is being exposed to this in his training now. Hopefully, the word interdisciplinary, will apply to the intellect of one oncologist, rather than to a group of specialists each applying his monocular vision to the patient's problem. . . .

"Ideally all out-patient oncology should be done in one facility. This allows for optimum use of laboratory and therapy technicians, oncology nurses and receptionists. . . .

"There is also the need for a visible team, to whom regional physicians may relate. The team must be accessible to all community physicians. It must be willing to help a referring doctor in any way he wants help, from simple consultation to total care of the referred patient. It is suggested that patients be seen by referral only, since this avoids the problem of competing with practicing physicians of the region, but more importantly it keeps [physicians and team members] in touch through phone calls and correspondence. . . .

"The oncology team can provide adequate coverage to allow time off for education and recreation. Someone taking weekend calls who knows the problems of cancer, while not an expert in all its treatment modalities, is superior to, say, a general radiologist who may have little knowledge of or interest in cancer patients. . . .

"Quality patient care must be one of the primary goals of the oncology group. Fully trained and qualified medical oncologists and therapeutic radiologists should be on the team. The minimum work load should be able to support one of each. Otherwise cancer practice should be done under the supervision of fulltime oncologists at the next larger town. In 1975, it is difficult to justify cancer management being done by physicians who are using 1965 methods. It is hard to keep abreast of oncology on a part-time basis. This is not to say there is no role for part-time oncologists. It is to say there should be a full-time person to whom the others can relate.

"Quality must carry over to the supporting staff. Good technologists, physicists, nurses and receptionists are worth their weight in gold (and are beginning to cost as much!). They help promote a high level of care."

M.H. Donaldson, of Philadelphia Children's Hospital, said in his presentation on management of pediatric neoplasms that a pediatric practice limited to oncology is not economically viable. His hospital serves a region with a population of several million and had only 116 new cases of pediatric cancer last year.

Since smaller communities obviously would not have even that number, physicians there should not be expected to develop the expertise in handling pediatric cancer cases that should be available at the larger centers. Referrals should be made to pediatric cancer centers, at least for initial treatment and planning, Donaldson said.

Local physicians should be encouraged to collaborate with the centers, Donaldson said. His hospital also has developed an outreach clinic which sends treatment teams to community hospitals.

SEVENTEEN CREG PROJECTS, MOST WITH MULTIPLE AWARDS, PLANNED

Seventeen project announcements covering seven research areas will be included in the June 1 publication of NCI's proposed Cancer Research Emphasis Grant programs. The 17 projects are budgeted for $4.1 million.

The seven areas designated as suitable for CREG are viral oncology, in vitro carcinogenesis, nutrition, tumor immunobiology, cell kinetics, epidemiology and communications.

The 17 projects, with the funds available for each, follow (multiple awards are planned for each unless otherwise noted):

Replication of RNA tumor viruses, $500,000; genetics of RNA tumor viruses, $350,000; in vitro chemical carcinogenesis, $400,000; epidemiology of cancer of the esophagus, $100,000; frequency of cancer in genetic isolates, $240,000; risk of human cancer in heterozygotes with recessive mutant genes predisposing to cancer in the homozygote and hemizygote states, $340,000.

Is Hodgkin's disease a communicable disease? $150,000; assessing the effects on offspring of preconception and inutero immunosuppression, $100,000; surveillance for drugs that may be carcinogenic, $250,000; long-term health sequelae of estrogen replacement therapy, $100,000; development and study of the avian model for ovarian tumors, $40,000 (single award).

Cancer epidemiology in collaboration with the NCI program of cancer surveillance, epidemiology and end results (SEER), $450,000; bedside approach to the etiology of cancer, $250,000; investigation of cancer research information transfer mechanisms, $350,000;

cell kinetics (2-3 awards), $200,000; role of glycoprotein shedding from mammary carcinoma cells in the spread of metastasis (2 awards $75,000 each), $150,000; and methodology for performing mass radiomammography with less than 150 mR per exposure (single award), $150,000.

The *NIH Guide for Grants and Contracts* with details of these announcements will be published about June 1. Applications must be submitted to the NIH Div. of Research Grants by Oct. 1 for January study section review and March, 1976, review by the National Cancer Advisory Board.

A second round of CREG announcements is being prepared for publication Sept. 1. Those applications would go to the June, 1976, NCAB.

The Div. of Research Resources & Centers plans to propose the molecular control program as a suitable area for CREG in a future announcement.

Benno Schmidt, chairman of the President's Cancer Panel, said at this week's meeting of the Panel that he had "grave misgivings" over including some of the seven research areas in the program. Much of that basic research should be funded through the regular grant mechanism, he said, rather than "trying to target something that shouldn't be targeted."

"That's just the point of CREG," Panel member Lee Clark said. NCI Director Frank Rauscher said the intent was to encourage basic research in those areas.

"Creg was designed to move in the direction of more investigator-initiated research," Panel member Ray Owen said.

One problem NCI has to deal with involves a bureaucratic hangup at NIH headquarters. All grant applications go to the Div. of Research Grants, the grants management unit that is independent of the NIH institutes. DRG assigns the applications to an institute according to referral guidelines.

DRR&C Director Thomas King told the Panel that strict adherence to the referral guidelines would result in most of the first round of CREG applications going to the other institutes.

"Why don't we just tell them to assign those to us?" Rauscher asked.

Samuel Price, who is coordinating CREG for the NCI divisions, said NIH has not yet agreed to do that.

"That's nonsense," Rauscher said. "Just tell them to do it."

James Peters, director of the Div. of Cause & Prevention, commented that "some of the other institutes would like to skim the cream from this program," suggesting they would keep the best of CREG applications if they could get their hands on them.

Another problem left unsettled is how to include commercial research organizations in the program. Since HEW prohibits grant awards to for-profit firms, they are not eligible for CREG as it now stands. NCI is negotiating with HEW to resolve that matter.

ABSTRACTS OF OUTSTANDING PAPERS FROM AACR MEETING

The program committee for the 66th annual meeting of the American Assn. for Cancer Research singled out 29 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list; the others will appear in a subsequent issue of **The Cancer Letter.**

THE EFFECT OF 6-MERCAPTOPURINE (6MP) ALONE AND IN COMBINATION WITH PREDNISONE IN LYMPHOCYTIC LYMPHOMA – ***John Louis, Christ Community and St. Joseph Hospitals, Chicago***

The effects of 6MP in lymphocytic lymphoma are not generally acknowledged. During the past 11 years, 73 patients, histologically diagnosed, were treated via a table of random numbers by one of four regimens: 6MP 2.5 mg/kg with (A) and without (B) prednisone and 6MP 1.5 mg/kg with (C) and without (D) prednisone. All were stage 4. Disease duration before 6MP therapy was .6 – 9.0 (median .75) years, ages ranged 23 – 79 (median 61) years, 31 were female and 36 did not receive prior therapy. The objective response rates were: A 12/18 (.66), B 11/23 (.47), C 12/17 (.70) and D 8/15 (.53).

Complete remission rates were: A 3/18 (.16), B 3/23 (.13), C 2/17 (.12) and D 2/15 (.13). Duration of response ranged from 23 days to 11 years (median 5 months). Duration of 6MP therapy (percentile) was 23 days (90), 54 days (75), 3.6 months (50), 10.2 months (25) and 1.5 years (10). Toxicity interrupted therapy after 21 days in 10/38 receiving 2.5 mg/kg, and 0/29 receiving 1.5 mg/kg; and after 42 days in 21/34 given 2.5 mg/kg and 1/25 given 1.5 mg/kg. Survival time from onset of disease (percentile) was: 6 months (90), 11.8 months (75), 2.6 years (50), 5.5 years (25) and 10 years (10). There can be little doubt 6MP has therapeutic effect in lymphocytic lymphoma.

MECHANISM OF ACTION OF BISCHLOROETHYLNITROSOUREA – ***Wayne Cowens, Robert Brundrett and Michael Colvin, The Johns Hopkins Oncology Center***

The aqueous decomposition of bischloroethylnitrosourea (BCNU) and cyclohexylnitrosourea (CCNU) generate organic isocyanates which carbamoylate the lysine residue of proteins. It has been suggested that this is the mechanism of the cytotoxicity of these compounds. We have recently demonstrated that the aqueous decomposition of BCNU and CCNU also generates volatile products which appear to be derived from a chloroethylcarbonium intermediate. We have now studied the aqueous decomposition of 1-(2-chloroethyl)-1-nitrosourea (CNU), an analogue of BCNU with similar activity against murine L1210 leukemia. This agent does not form an organic isocyanate on aqueous decomposition, but does yield the same spectrum of volatile products as BCNU and CCNU.

These findings support the thesis that decomposition to alkylating chloroethylcarbonium intermediates is responsible for the antitumor activity of these compounds. We have prepared a new agent, 1-(2-chloroethyl)-3,3-dimethyl-1-nitrosourea (DCNU), which is stable in aqueous solution. This agent is as effective against L1210 leukemia in vivo as BCNU, but unlike BCNU, is not active in vitro. Our data indicate that DCNU is metabolized in vivo to a more labile nitrosourea.

ON ERRORS IN DNA REPLICATION AND CARCINOGENESIS – ***Lawrence A. Loeb, Michael A. Sirover, Lisa Weymouth and Narayana Battula, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia***

To explore the relationship between errors in DNA replication and malignancy, we have studied the fidelity of DNA synthesis by cellular and viral DNA polymerases and the effect of a chemical carcinogen on this fidelity.

Our initial observation that avian myeloblastosis virus DNA polymerase is error prone when copying polynucleotide templates has been extended to the DNA polymerases of two other RNA tumor viruses, Rauscher leukemia virus and Rous sarcoma virus. For example, with poly (rA) .oligo (dT) as a template each of these enzymes erroneously incorporates one molecule of dCTP for approximately every 600 molecules of dTTP polymerized.

Treatment of the polynucleotide template poly (dA) .oligo (dT) with the mutagen and chemical carcinogen *B*-propiolactone (BPL), increases these errors in DNA synthesis. Studies using ^{3}H-labeled BPL, demonstrate that with progressive modification of the template, there is a progressive increase in the number of non-complementary nucleotides incorporated when the modified templates are copied by DNA polymerases from RNA tumor viruses or from sea urchin nuclei.

The infidelity of DNA polymerases from tumor viruses suggests that such enzymes may be mutagenic during viral and host cell replication. The above analysis may provide an in vitro model system for screening potential mutagens and carcinogens.

METABOLISM OF CYTOSINE ARABINOSIDE (ARA-C) IN VITRO BY NORMAL AND LEUKEMIC BLOOD AND BONE MARROW – ***Ting-Chao Chou, Bayard D. Clarkson and Frederick S. Philips, Memorial Sloan-Kettering Cancer Center, New York***

Blood of normal and leukemic and bone marrow aspirates of leukemic human subjects were incubated in Eagle's basal medium containing tritiated ara-C in the presence and absence of tetrahydrouridine (THU). Nucleosides and nucleotides in acid-soluble extracts were fractionated with anionic exchange columns. Nucleotide fractions were also hydrolysed to nucleosides for analysis of deaminated products. Deamination was negligible in normal blood whereas leukemic blood and marrow samples deaminated ara-C to a variable extent. Deamination of ara-C was inhibited by THU. Relatively little radioactivity was found in mono- and di-phosphate nucleotides fractions; the levels were not appreciably affected by THU. Among the various leukemic samples and normal blood studied, only acute myelocytic and meylomonocytic leukemia (AML and AMML) showed increased (1.5 –5 fold) levels of triphosphate nucleotide in the presence of THU. The radioactivity in the triphosphate fractions contained over 90% ara–CTP.

These results indicate that in AML and AMML the presence of THU can induce net increases in the accumulation of the active metabolite, ara-CTP, and suggest the possibility that the combined use of THU and ara-C might have increased anti-leukemic efficacy in these types of leukemia.

INDUCTION OF ORNITHINE DECARBOXYLASE AND S–ADENOSYL–L–METHIONINE DECARBOXYLASE IN MOUSE EPIDERMIS BY TUMOR PROMOTERS – ***T.G. O'Brien and R.K. Boutwell, McArdle Laboratory, Univ. of Wisconsin***

As part of an effort to discover what specific functional changes in mouse epidermis are relevant to tumor promotion, we have examined the response of epidermal ornithine decarboxylase (ODC) and S-adenosyl-L-methionine decarboxylase (SAMD) to a single topical application of croton oil or of phorbol esters of varying promoting abilities. The enzyme activities were measured in post-mitochondrial supernatants from mouse epidermis. Croton oil or 12-0-tetradecanoyl-phorbol-13-acetate (TPA) treatment stimulated ODC activity, beginning about 2 hours after application, reaching a peak (250-fold greater than control after TPA) at 4-5 hours and declining rapidly to control level by 9-12 hours. SAMD activity also increased soon after treatment. The increased enzyme activities after TPA treatment were dose-dependent; the magnitude of the stimulation was correlated with the promoting ability of the doses. Similarly, the response of the enzymes to phorbol didecanoate and phorbol dibenzoate (a moderate and a weak promoter, respectively) correlated with promoting ability. The non-promoters phorbol and phorbol diacetate were without effect. These results suggest that the specific induction of ODC and SAMD activities may be essential for tumor promotion.

ON THE ABSENCE OF SPECIFIC mRNA SPECIES IN HEPATOMA CELLS – ***P. Feigelson, L.R. Murthy, A. Sippel and H.P. Morris, Institute of Cancer Research, Col. of Phys. & Sur,, Columbia Univ.***

Basal and hormonally induced levels of tryptophan oxygenase (T.O.) were present in host livers, but absent in hepatomas 7793, 5123C, 5123D. It was, therefore, of interest to explore whether the loss in the ability of hepatomas to synthesize certain hepatic proteins like T.O. and their inability to respond to hormonal control, represents a transcriptional or translational deficiency. mRNA from the livers of hosts bearing any of the three tumor strains, but not

from their corresponding hepatomas, direct, in a cell-free translational system, the synthesis of radioactive subunits of T.O. as identified by immunoprecipitation and SDS-polyacrylamide gel electrophoresis of the solubilized immunoprecipitate. The mRNA from host livers, but not their hepatomas, showed enhanced rates of synthesis of T.O. after hydrocortisone administration. Thus, all three Morris Hepatomas are devoid of detectable levels of functional mRNA for T.O. under basal and inducing conditions. 5123D hepatomas lack and livers of their male hosts contain the mRNA for α2u globulin, an urinary protein synthesized under androgenic control in the liver. In hepatomas, the genes for T.O. and α2u globulin have either been cytogenetically deleted or more probably are in a transcriptionally silent state preventing the synthesis of the corresponding mRNA and consequently that of the protein.

PROTEIN KINASE AND ITS REGULATORY EFFECT ON REVERSE TRANSCRIPTASE ACTIVITY OF ROUS SARCOMA VIRUS – ***S.G. Lee, R.A. Jungman, and P.P. Hung, Northwestern Univ. Medical School, and Molecular Virology Lab, Abbott Labs, North Chicago.***

It has become apparent that the activity of nucleic acid polymerases may be controlled through enzymatic phosphorylation and dephorylation. We have studied the effect of protein phosphokinase (PK) and phosphoprotein phosphatase on reverse transcriptase (RT) activity of Rous sarcoma virus (RSV). PK from RSV-transformed chick embryo fibroblasts was purified by DEAE-cellulose chromatography, Sephadex gel filtration, and isoelectric focusing. Purified RT from RSV was incubated with PK and ATP under conditions allowing incorporation of phosphate into substrate proteins. Subsequently, RT activity was assayed in the presence of poly(rAdT) as template. A 2 to 5-fold increase of RT activity was found when RT was preincubated with active PK and ATP. Incubation of RT with heat-treated, inactive PK and [γ-^{32}P]ATP and subsequently purified by chromatography on phosphocellulose, 32p-labeled protein was found in those fractions with RT activity suggesting 32p incorporation into RT or RT-associated proteins. A 50 to 200% decrease of RT activity was observed after incubation of RT with phosphatase. The results suggest that phosphorylative modification of RT may be critical in the regulation of RT-catalyzed DNA synthesis.

RELATIVE RATES OF ALTERNATIVE PATHWAYS OF PURINE NUCLEOTIDE BIOSYNTHESIS IN EHRLICH ASCITES TUMOR CELLS IN VIVO – ***Camilla M. Smith and J. Frank Henderson, Univ. of Alberta Cancer Research Unit and Dept. of Biochemistry, Edmonton, Alberta, Canada***

Several alternative pathways of purine nucleotide synthesis coexist in cells – purine biosynthesis de novo, the purine phosphoribosyltransferases, and adenosine kinase. However, the relative importance of each pathway for maintaining purine nucleotide concentrations in cells is not known. In this study, specific inhibitors were used to block these synthetic routes in Ehrlich ascites tumor cells in vivo, singly and in combination. The effect of inhibiting each pathway was evaluated by measuring intracellular purine nucleotide concentrations by high speed liquid chromatography. Purine biosynthesis de novo was inhibited by azaserine, 6-*O*-benzylinosine was used to inhibit hypoxanthine-guanine phosphoribosyltransferase, mycophenolic acid inhibited inosinate dehydrogenase, hadacidin was used to inhibit adenylosuccinate synthetase, adenosine kinase was inhibited by either 4-amino-5-iodo-7-*B*-D-ribofuranosyl pyrrolo (2, 3-*d*) pyrimidine or 6-*N*-phenyladenosine, and phosphoribosylpyrophosphate synthesis was inhibited by xylosyl adenine. The results indicate that purine nucleotide concentrations of Ehrlich ascites tumor cells are maintained primarily by purine biosynthesis de novo; the other pathways are quantitatively less important.

CHEMOTHERAPY OF ACUTE MYELOCYTIC LEUKEMIA WITH NEURAMINIDASE TREATED ALLOGENEIC LEUKEMIC CELLS – ***J.G. Bekesi, J.F. Holland, J.W. Yates, E. Henderson and R. Fleminger, Mt. Sinai School of Medicine, New York, Roswell Park Memorial Institute, Buffalo.***

We previously reported successful chemoimmunotherapy with vibrio cholerae neuraminidase (VCN) treated leukemic cells in the cure of DBA/2 mice with L1210 and AKR mice with spontaneous leukemia. This treatment evokes greater resistance to challenge than any other reported chemotherapy in experimental leukemia.

These data led to clinical trial in acute myelocytic leukemia using VCN treated allogeneic mycloblasts. Patients were allocated to two groups following successful remission induction using cytosine arabinoside and daunorubicin. All received cyclical maintenance chemotherapy every 4 weeks with VCN treated allogeneic myeloblasts; i.d. Immunologic monitoring included recall antigen skin testing, T & B lymphocytes and lymphoblastogenesis. In each immunization 10^{10} VCN cells were injected in approximately 50 sites in different node drainage areas. Induration to VCN treated cells at 48 hours was proportional to cell number per site and increased with frequency of immunization, diameters usually exceed 25 mm. In ten patients who received previous antileukemic therapy, six immunized patients had more than twice the remission duration of controls. In previously untreated patients the median remission duration on chemotherapy alone was 20 weeks for 7 patients, while 5 of 7 patients receiving VCN immunotherapy remain in remission from 56 to 97 weeks.

MARROW TRANSPLANTATION IN ACUTE LEUKEMIA – ***E.D. Thomas for the Seattle Group, Univ. of Washington***

From 1969 to 1974 matched sibling marrow transplants were done for treatment of 40 patients with ALL and 40 patients with AML after failure of extensive chemotherapy. Of patients prepared with 1,000 rad total body irradiation(TBI) 4 with AML died too soon to be evaluated. Six with ALL had successful grafts, 5 had recurrent leukemia, in 2 the recurrence was in donor cells. One patient is in remission on no therapy at 4½ years. Seventy patients were prepared for grafting with cyclophosphamide, 60 mg/kg x 2, and TBI. Of transplants done prior to 1974, survival beyond 1 year was 5/22 with ALL and 5/23 with AML with longest survivors now at 3 and 2½ years. The 14 patients transplanted in the first half of 1974 show a median survival now greater than 7 months. The major cause of death was graft-versus-host disease and interstitial pneumonia due to cytomegalovirus. Leukemia has recurred in 8 of 34 patients with ALL and 7 of 36 with AML. The median time to relapse was 90 days but 6 relapsed in less than 6 weeks. Recurrence took place despite a functioning marrow graft with no correlation with graft-versus-host disease. The remarkable resistance of some of these leukemias to high dose chemotherapy and TBI may have been related to duration of disease and previous extensive therapy suggesting the desirability of earlier marrow transplantation.

THE EFFECT OF INTERFERON ON EXOGENOUS AND ENDOGENOUS MLV INFECTION – ***Paula M. Pitha and Wallace P. Rowe, The Johns Hopkins Oncology Center, and NIH***

The effect of purified mouse interferon on the replication of mouse leukemia virus (AKR-L1 strain of MLV) in the clonal line of AKR cells was studied with main emphasis on the determination of whether interferon exhibited a differential effect on the replication of exogenous virus, activation of endogenous virus by IdRrd, and chronic virus production. It was found that interferon inhibited replication of the virus in all these systems. Interferon treatment did not abort exogenous infection or virus induction by IdUrd, but only delayed appearance of infectious virus. Virus production by chronically infected cells was also suppressed in the presence of interferon; however, after removal of interferon, rapid recovery of virus production occurred. Under conditions where interferon treatment significantly inhibited virus yield (as measured both by infectious virus and virion-associated reverse transcriptase activity), no significant inhibition of synthesis of virus specific (gs) antigen was observed (as measured by immunofluorescence and radioimmunoassay for p30 protein). Thus these results indicate that, unlike its effect on the majority of lytic viruses, interferon inhibits one or more of the later steps in the MLV replicative [redacted] which occur after the expression of viral gs antigen.

A RETINOIC ACID BINDING PROTEIN OF CHICK EMBRYO METATARSAL SKIN – ***Brahma P. Sani, Kettering-Meyer Laboratory, Southern Research Institute***

Retinoic acid (RA), which reverses metaplastic changes caused by chemical carcinogens in vivo and in organ culture, may act as a hormone by regulating gene activity. We have found a specific RA-binding protein which may be involved in the expression of its biological effect. The protein has a molecular weight of 20,000 and an isoelectric pH of 4.6. Competition experiments with 200-fold excesses of unlabeled RA, retinol, retinal, methyl retinoate, ethyl retinamide, synthetic analogs of RA and γ-linolenic acid reveal that only RA and its analogs with a free carboxyl group bind to this protein. Among the analogs of RA, a cyclopentene analog, a trimethylmethoxyphenyl analog, 13-cis-RA and a-RA compete for the binding site on the protein, with the cyclopentene analog having greater affinity than RA. Phenyl and pyridyl analogs of RA are poor binders. In general, the ability of the various analogs to bind to this protein correlates with their biological activity in the reversal of keratinization and in the production of mucous metaplasia by chick embryo metatarsal skin.

CONTRACT AWARDS

Title: Eleven additional construction taks at Frederick Cancer Research Center
Contractor: Litton Bionetics, $237,125.

Title: Testing for cytotoxicity of chenical agents
Contractor: Univ. of Miami, $116,289.

Title: Development of a tissue culture transformation system
Contractor: Columbia Univ., $191,830.

Title: Administrative and technical support services for conferences and seminars
Contractor: DOT Systems Inc., $548,875.

SOLE SOURCE NEGOTIATIONS

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

Title: Study of the effects of anticancer agents on reproduction
Contractor: Dow Chemical Co.

Title: Efforts to develop new prognostic and therapeutics modalities based on basic studies on cell transformation and on transformed cells
Contractor: Litton Bionetics.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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