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CANCER CONTROL CONTRACTORS SEVERELY CRITICIZED IN MERIT PEER REVIEW; INADEQUATE REPORTS CITED

Merit peer review of ongoing contracts, recently ordered by NIH to provide closer monitoring with the aid of outside advisors of contract-supported research, last week revealed some potentially serious shortcomings in performances by a number of organizations supported by NCI's Div. of Cancer Control & Rehabilitation.

DCCR conducted three merit review sessions—by the Cancer Control

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In Brief

NCI FUTURE BUDGET PLANNING NOW IN OPEN; ONE OR TWO COMP CENTERS IN 12-18 MONTHS

SECRET BUDGET discussions by government staff with public advisory groups apparently are no longer legal, at least according to the latest HEW interpretation of the Freedom of Information Act. As a result, NCI's fiscal 1978 budget projections will be discussed at an open meeting of the National Cancer Advisory Board's Subcommittee on Planning, scheduled for June 21, 7:30 p.m. (see meeting notices, inside). This will be a major step in developing the budget NCI will submit to the President. In the meantime, the 1977 fiscal year amount for NCI will be largely determined when the Senate HEW Appropriations Subcommittee marks up its bill next week. Unless the Senate adds a substantial amount over the House figure (which was $773 million, an increase of only $11 million over 1976), it will be a no-growth Cancer Program next year. . . . **ONE OR TWO** more comprehensive cancer centers will be named within the next 12 to 18 months, NCI Director Frank Rauscher told the President's Cancer Panel. He didn't say it, but UCLA almost certainly will be one. New York Univ. is next in line at present, but that could change. . . . **GARY FLAMM**, assistant director of NCI's Div. of Cancer Cause & Prevention, will be delegated much of the responsibility for running the Carcinogenesis Program with the resignation of Umberto Saffiotti. . . . **BENNO SCHMIDT** told the Panel that two of the new members of the National Cancer Advisory Board "are distinguished scientists in the field of environmental carcinogenesis, which should make it apparent there is no tendency to diminish emphasis on environmental carcinogenesis. On the contrary, NCI will be getting the best scientific and professional advice on how best to spend its money. I don't think $134 million (the amount NCI estimates is spent in that area) is a weak allocation" . . . . **LEE CLARK**, Panel member and President of the Univ. of Texas System Cancer Center, said that foreign health leaders believe the development of comprehensive cancer centers is one of the more notable achievements of the Cancer Program. He said there are 25 to 40 such centers elsewhere in the world, either in place or in planning stages. West Germany is planning to develop 10, with the first in Heidelburg.

DCCR CONTRACTORS FAIL TO IMPRESS REVIEWERS WITH REPORTS, PERFORMANCE

(Continued from page 1)

Community Activities Review Committee, Intervention Programs Review Committee and Supportive Services Review Committee. All three committees are made up entirely of non-government professional and lay experts, and were assisted by teams of consultants. They did not pull their punches.

The contractors were asked to provide summary reports of the conduct and results of the projects to date, following the format of the approved proposals and scope of work. The review committees found that most of the reports were incomplete, did not respond to questions asked, and were otherwise inadequate.

"If their final report is as bad as this one," commented a reviewer on one evaluation, "I don't see how the contract can be renewed. I have the feeling they have performed well in most of the project areas, but how can we know? The information isn't here."

Many of the contracts reviewed will expire within a few months. Reviewers questioned the advisability of holding the merit review now. "This should have been done in mid-term of the contract period," said one. "We can't have much of an impact on the programs now." Merit reviews in the future are planned for mid-term, but initiation of the system now required that the expiring contracts be reviewed immediately.

One benefit might be that contractors—many of them involved for the first time in an NCI-supported program—will learn from the interim review what is expected in the final reports. Here are some criticisms of the interim reports:

- No indication of the number of patients seen (under a contract for establishing integrated cancer rehabilitation services). No follow up data. No evaluation. "There's nothing to show what happened. Something may have happened, but you couldn't tell it from the report," said one reviewer.
- "It's ridiculous that they can get money by writing a gobbledygook report like this. Anyone could write that without going near the program."
- "The only hard fact they have included is that they have demonstrated they can stage meetings."
- "How on earth did they get this through peer review in the first place?"
- "The entire report is confusing, with no hard data. We need facts, not flowery prose."
- "They have got to be specific. We have no idea of what types of patients they have been seeing. Breast cancer, GI, head and neck cancers, all involve different types of rehabilitative services. How about terminal patients? That requires a totally different type of service, but we aren't given that information."
- This report tells an awfully good story, but we don't know what services were rendered, what happens to patients after they leave the hospital, how many were referred to special services. What did they do with all that money they got?"
- "On the basis of this report, I can't recommend the contract be continued, or even continued with conditions. We need specific information on approaches. We need to know what is going on."
- "It's an affront to us. We gave them a document (a list of questions to be answered) which spelled out what we wanted. They skipped around, answered only those questions they wanted to. I'm flabbergasted."
- "As much as I would like to give them a chance, I favor cutting them off if they don't come through with the information we want."

Most of the contracts reviewed were initiated in the early days of the Cancer Control Program, when NCI staff, project officers and contract specialists were trying to organize the program without clear concepts of goals and direction. Tighter management and development of a better understanding by NCI staff of what control and rehabilitation are supposed to achieve should result in better directions to contractors.

The reviewers found a lot to criticize in performance, as well as the inadequate reports. Some examples:

- "The project staff was unable to influence attending physicians."
- "There was virtually no evaluation, and very little coordination with other hospitals. Outside organizations, other than the American Cancer Society, were not involved. They're just providing a service, not a demonstration."
- "Coordination involved just the rehabilitation team members. They didn't understand their roles as coordinators."
- "I don't get the feeling from the report about management approaches. There's no concept of cooperation by physicians in the network hospitals. I'm not sure all the patients reported in the program are really there."
- We have nothing to indicate the offeror has complied with the terms of the RFP. One definite requirement is an adequate number of patients. There's nothing to indicate that. Also there is nothing to indicate that a network has been established."
- "The response was along the lines of their own goals, not that as outlined in the guidelines. They're doing something that wasn't included in the project, and apparently are getting away with this freewheeling."

In one instance, committee members were considerably impressed by the performance of a contractor, but the consultant who reviewed the report rated it "poorly and not in compliance" with the RFP.

The contract was awarded to develop an integrated team approach in providing rehabilitation services. The principal investigator, "well known, well liked," turned the job over to a "mature, charming nurse

oncologist," the committee reviewer said.

"The nurse could not be intimidated. She made this program work, with her enthusiasm and administrative ability." Working with other nurses, she developed their support and helped educate them in rehab services. The number of patients receiving such services increased substantially, and participation of private practicing physicians also increased. The number of hospital days per patient was decreased.

But the consultant, while agreeing that the work of the nurse coordinator was impressive, insisted that the intent of the contract was "totally ignored." Part of the proposal included defining ongoing evaluation that was to be made, but the evaluation process was stopped early in the contract period "because we felt very good about what we were doing."

"They abandoned evaluation. . . . They got an effective nurse coordinator, and NCI got nothing in terms of development of coordinated rehabilitation services."

Contracts reviewed last week by DCCR were:

Community Activities—Integrated Cancer Rehabilitation Services; Training Programs for Maxillofacial Prosthodontists/Dental Technicians; Demonstration of a Cancer Rehabilitation Facility and/or Department; and Cancer Training Programs for Physical and/or Occupational Therapists.

Intervention Programs—Prototype Network Demonstration Projects in Breast Cancer, and Implementation of Cervical Cancer Screening Programs.

Supportive Services—Nursing Oncology Program; Telephone Cancer Information System; and Comprehensive Cancer Center Communications Network.

DCCR outlined how it expects merit peer review to operate.

The term merit peer review as used in DCCR refers only to the technical merit review of ongoing contract-supported projects currently being carried out by the division. The review will be referred to the appropriate technical review committee, or combinations thereof, and will be managed by the Office of Committee and Review Activities (OCRA).

The purpose of a merit peer review is to evaluate the progress of ongoing DCCR contract projects through the perr review process. The information gained from this review will assist DCCR and its project officers in the assessment of project effectiveness and, in some instances, committee recommendations will assist DCCR in the determination of contract termination.

The following are the conditions under which merit review by a DCCR technical review committee may be initiated:

Mandatory Condition

Mandatory fulfillment of the DCCR policy requirement of merit peer review on all ongoing contracts at least once during the lifespan of each contract. (An exception to this requirement may be made in those cases where the contract duration is less than two years). DCCR intent to perform a merit review will be included in the RFP; in all contract agreements; and will be discussed during contract negotiations. As much flexibility as possible in the timing of the merit review will be allowed, so that the review will be conducted when it will be most advantageous both for the contractor and DCCR.

Optional Conditions

A. A merit peer review of an individual project or a group of projects may be requested by the DCCR director and/or the project officer (with the concurrence of the appropriate branch chief and associate director) at any time during the lifetime of the contract, if such a review seems warranted.

B. The Cancer Control & Rehabilitation Advisory Committee (CCRAC) may, on the basis of questions and issues raised at the time of the program reports made to it periodically by DCCR staff, advise that a merit peer review be conducted to assess the progress of one or more contract projects and that a report of that review be brought back to the CCRAC.

If the merit peer review is conducted on the basis of advice from CCRAC, representatives from that committee will be invited to participate as consultants to the review committee at the time of the committee meeting and to participate in site visits.

C. A merit peer review may be requested at the completion of the contract period on all contracts issued under a single RFP. Such a review will not only assist the division in determining how well the contract requirements were fulfilled, but will provide an independent assessment of that program area and guide program staff toward those program thrusts which should be continued, expanded, discontinued, or initiated. This type of review would be particularly appropriate at the completion of contracts involving field tests and demonstration projects for the purpose of evaluating their success and to advise on future DCCR action.

D. The contractor may request a merit peer review.

The operational procedures for reviews will be those exercised in traditional peer review and are essentially the same as for pre-award reviews, except in the following aspects:

1. Referral for Review—OCRA after consultation with appropriate program staff will refer the projects for review to one of the three DCCR technical review committees or some combination thereof. Preferably, the committee which conducted the pre-award review will be involved in the merit review. The initial reviewers will be similarly involved where possible. There are instances where a DCCR technical review committee may be combined with a technical review committee from another division in NCI. Consultants from the scientific community at large or from other federal technical review committees will be used as necessary.

2. The chief of OCRA will direct a letter to the

contractor to the effect that a peer review will be undertaken. The letter will include a statement of the purpose of the review, the name of the committee which will undertake the review, and the name of the executive secretary who will thereafter communicate directly with the contractor on all matters relevant to that merit review.

3. The executive secretary of the assigned technical review committee will, with the assistance of the project officer, the associate director, and branch chiefs, draw up a clear statement of the purpose of the merit review and the specific charge to the committee. The executive secretary will review this statement with the chairman of the committee, after which it will be transmitted to the committee members.

The executive secretary will accumulate the materials needed for review from the following individuals at least one month before the scheduled review:

1. The contract specialist will provide a copy of the original RFP, the approved proposal and the final scope of work as it was negotiated in the contract, and any pertinent facts about the contract which are relevant to the review.

2. The project officer will provide: (a) A summary of his assessment of the progress to date. This summary should refer to the specific approved proposal and scope of work negotiated into the contract. (b) Copies of all contractor progress reports, project officer reports, project visit reports and a final report (where appropriate), as well as any important correspondence or telephone conference reports.

3. The contractor will be asked to provide a summary report of the conduct and outcomes of the project to date in terms of the format of the approved proposal and negotiated scope of work. He will be invited to discuss with the project officer any other materials which he feels are relevant for the purposes of the merit peer review. With the concurrence of the executive secretary and chairman of the assigned technical review committee, the latter may be introduced into the review process at the same time as other review materials.

4. The executive secretary will prepare a merit review criteria sheet which will reflect the purpose of the review and the charge to the committee. Where appropriate, these criteria will parallel the original pre-award criteria. This sheet will be distributed to the committee in the usual manner or to the site visitors as necessary.

There are three types of site visits which may be made in conjunction with the merit peer review of ongoing contracts.

1. A site visit will be conducted on the basis of the recommendation of the technical review committee made during the initial merit review meeting. The site visit will be conducted for the purposes of clarification, additional information or to assess program facilities. Specifically, the questions and issues raised at the initial review will be discussed. The visitors may provide advice and guidance should the occasion arise. In the event that such a site visit is conducted, a follow-up report on that visit should be made to the committee at the subsequent meeting. The committee will then make its final recommendations.

2. A reverse site visit may be conducted at the time of the review meeting in instances where, in the opinion of the DCCR director and the project officer (with concurrence by the appropriate branch chief and associate director) there is a question of contract termination due to apparent critical deficiencies in meeting contract requirements. Such a site visit must also be concurred in by the executive secretary and chairman of the appropriate technical review committee. In such cases, the principal investigator and his associate may make a presentation before the technical review committee and respond to questions. The number of representatives of the contractor should not ordinarily exceed three or four and are selected by the contractor with the concurrence of the executive secretary of the committee and with the advice of the project officer.

3. A site visit may be made in advance of the review meeting on those few occasions when information which is critical for merit review cannot be obtained in any other way. The need for such a visit is determined by the executive secretary of the appropriate review committt on the advice of the project officer (with the concurrence of branch chief and associate director). This site visit will be managed by the executive secretary in the same way as a committee-recommended visit.

NCI AGREES TO OFFER RFP FOR NEW DRUG SCREEN SYSTEM "IN THE FUTURE"

The Drug Development Contract Review Committee advises NCI's Div. of Cancer Treatment on a variety of matters pertaining to drug development, not limiting itself merely to contract reviews. Much of the advice from the relatively new committee has been unsolicited, but after an initial period of grumbling about it, DCT staff has more or less become reconciled to at least living with the advice, if not always accepting it.

Led by Emil Freireich, outspoken chief of developmental therapeutics at M.D. Anderson, the committee last fall questioned the efficacy of the Drug Development Program's screening systems and asked that an RFP be issued seeking proposals for new methods of finding compounds with anticancer activity.

Saul Schepartz, director of the program, defended his screening systems but agreed to study the suggestion. At the committee's meeting last month, Schepartz said the proposal had been approved "for future year funding—in general, we agree, we will do it."

Freireich explained his plan. "If we have 10,000 compounds being submitted, couldn't we just say in

the RFP, here's what we have, now how would you screen them? Then review the proposals. My feeling is that we would get many new creative ideas."

Freireich said that the primary screen should be removed from the category of a service function and be considered a research function . . . Screening should be a scientific activity."

Freireich said that "from the clinical point of view, the screen is not a screen, it's an insurmountable wall." He said the screen seems more concerned with keeping compounds out when it should be more important not to miss any. "Why must we always assume that a negative result should drive the system?"

Schepartz explained that the objective of the screen is to select materials most worthy for further development. "We assume we can't test everything clinically, and must test some in small animals. We have a minimum of false positives and false negatives. How minimum? We set limits, so at least we get the statistical significance of what's observed. We try to devise systems so that we spend as little effort as possible on the large number of compounds that show no activity, and place emphasis on those that do show activity."

"But we always set the screen up so that compounds fall out," Freireich said. "There's more chance for false negatives than for false positives."

Schepartz disagreed. "We intentionally set a lower limit, to eliminate false negatives."

Freireich insisted that "there's no question that the number of compounds available for clinical tests is far below the capacity of the program to develop new compounds and the willingness of investigators to clinically test them."

"Do you have any basis to estimate the number of active compounds that have not been found?" asked Erich Hirschberg, chairman of the committee.

"Yes, the real evidence is that consistently and regularly we have found activity in compounds previously missed," Freireich said. "Of 50 compounds in clinical use, the great majority would have failed the screen."

Schepartz disagreed. "The vast majority would have come through with flying colors. Most of them are extremely active in the L-1210 system."

Committee member Robert Goldberger said, "It seems to me it is not relevant how many false negatives there are, and not what are we missing, but are we satisfied with what we're getting? How can we set up screens that are any better?"

"We're trying to squeeze a turnip," said committee member George Santos. "Maybe we don't have enough science."

Committee member Roland Robins suggested that a screening system be developed to test compounds for antiviral activity.

John Venditti, chief of the Drug Evaluation Branch, said, "We don't screen compounds now for antiviral activity. That's another program, another couple of million bucks."

ROGERS PUTS IN BILL AUTHORIZING BONUS, BUT IT WON'T KEEP RAUSCHER

Rep. Paul Rogers (D.-Fla.) last week introduced a bill that would give the HEW secretary authority to award as many as 25 bonuses, to a maximum of $15,000, to individuals in his department for meritorious service.

While the bill primarily was designed to keep NCI Director Frank Rauscher on the job, it probably would not accomplish that end. Rauscher needs at least $20,000 a year more than his present salary of $37,400, and in fact has said he could not afford to stay on for less than $60,000.

Not only is the $15,000 not adequate, but there is no guarantee that Rauscher would be one of the honorees, and even less certainty that he would receive the bonus year after year.

Rogers, chairman of the House Health Subcommittee, has been sitting on a draft of a bill which would raise the salaries of the NCI director, NIH director and director of the Heart & Lung Institute to $65,000. The White House and Civil Service Commission have agreed not to oppose the bill, and David Henderson (D.-N.C.), chairman of the House Post Office & Civil Service Committee has told Rogers he would not interfere as long as the raises were confined to individuals in the health field.

For some reason, Rogers has not put that measure into the hopper. Time is running out, and it is beginning to appear likely that Rauscher will be forced to accept one of several offers he has received outside of government, some of which will pay more than twice the $60,000 he is asking.

ABSTRACTS OF OUTSTANDING PAPERS PRESENTED AT ANNUAL AACR MEETING

The program committee for the 67th annual meeting of the American Assn. for Cancer Research selected 44 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list, chosen from sessions on carcinogenesis, biochemistry, virology, immunology, clinical investigations and experimental chemotherapy.

HORMONAL STIMULATION OF A VIRUS-RELATED ANTIGEN IN A HUMAN BREAST CARCINOMA CELL LINE, MCF-7 – H.D. Soule, C.M. McGrath, A. Long and M.A. Rich, Michigan Cancer Foundation

Sublines of MCF-7, a human breast carcinoma cell line (JNCI, 51: 1409, 1973) are inductible for an RNA tumor virus-like particle, 734B, (Nature, 252:247, 1974).

Since MCF-7 cells contain cytoplasmic, steroid hormone receptors (J. Biol. Chem. 248:6251, 1973) it was of interest to determine the influence of hormones on viral synthesis. 734B, the candidate human breast cancer virus, contains antigens which are cross-reactive with mouse mammary tumor virus (MuMTV) so that antisera containing multiple specificities reactive against MuMTV antigens could be used to detect synthesis of viral antigen using immunofluorescence tests.

The addition of progesterone stimulated a 20-fold increase in the synthesis of the cross-reactive antigens(s) in MCF-7 cells. The stimulation was dose-responsive and was maximum when progesterone was added to dividing cells. Other steroid hormones had no stimulatory effect. The antigens were detected in progesterone treated MCF-7 and MuMTV positive C3H tumor cells but not in human non-breast cell lines, nor in normal cells of murine and human origin. MCF-7 cells do not react with antisera against simian and murine type C particles.

These results suggest that MuMTV information exists in malignant human breast tumor cells and that expression of the information is stumulated by progesterone.

THE GENETICS OF RESISTANCE TO MAMMARY TUMOR VIRUS (MTV-S) IN C57BL/CRGL AND I/CRGL MICE – John Danilovs, Univ. of California (Berkeley)

Mendelian segregation of genes responsible for resistance to MTV-S was studied in crosses between highly resistant C57BL and I inbred mice. (C57BL X I)F_1 hybrids when foster nursed by MTV-S infected C3H females are highly susceptible to MTV-S infection and mammary tumor development. F_2, backcross, and second backcross females were foster nursed on C3H females and tested for some or all of the following traits presented in C3H fostered F_1 hybrids but not in C57BL$_f$C3H or I$_f$C3H parent strains: (a) ability to transmit viral infection to susceptible test animals via blood transfer, (b) ability to transmit viral infection at first parity to susceptible animals via milk, (c) appearance of viral antigen in milk detected by immunodiffusion, (d) development of mammary tumors, and (e) presence of hyperplastic alveolar nodules at autopsy (14 mo.). The results from backcrosses to the C57BL show segregation of one recessive gene (Mtv-1) which has a primary role in resistance to MTV-S infection and one or more genes operating after infection to reduce tumor incidence in infected animals.

Preliminary data suggest that Mtv-1 is linked to H-2. Backcrosses to the I suggest that two or more other genes are involved in that strain's resistance.

EVIDENCE FOR A PHYSICAL ASSOCIATION BETWEEN FRIEND VIRUS-INDUCED AND HISTOCOMPATIBILITY ANTIGENS ON LEUKEMIA CELL SURFACES – J. Eric Bubbers, Richard Steeves and Frank Lilly, Albert Einstein College of Medicine

The possibility that viral antigens expressed on Friend virus (FV)-induced leukemia cell plasma membranes are physically associated with murine H-2 antigens has been examined. Splenic erythroblasts from either BALB/c (H-2^d) or BALB.B (H-2^b) mice 7-14 days after infection with FV were susceptible to lysis mediated by antibodies directed against FV or appropriate H-2K and anti-H-2D antigens. Antigen redistribution through cap formation rendered these cells resistant to subsequent lysis mediated by the capping antibody. Experiments were performed in which cells capped in the presence of either anti-FV antiserum or normal mouse serum were used as targets against which anti-FV, anti-H-2K and anti-H-2D antisera were titrated. Whereas anti-H-2K antisera lysed the two cell populations identically, significant differences between the two populations in susceptibility to lysis by anti-H-2D antisera were observed. Anti-FV antibody capped target cells (H-2^b or H-2^d) required, on the average, a 50% greater concentration of anti-H-2D antisera to achieve the same degree of lysis as control cells. This apparent co-capping is interpreted as indicating that a portion of cell surface Friend virus antigens are physically associated with H-2D antigens.

"TUMOR-IMMUNE" RNA CONVERSION OF LYMPHOID CELLS OF TUMORED MICE FROM BEING UNRESPONSIVE TO RESPONSIVE UPON CHALLENGE WITH TUMOR SPECIFIC ANTIGEN – Donald Braun and Sheldon Dray, Univ. of Ill.

Balb/c mice grafted with MOPC-315 plasmacytoma tumor cells were assessed for the development and persistance of tumor-specific cell-mediated immunity (TS-CMI) by the in vitro cell-migration-inhibition microassay. When mice were grafted subcutaneously with $1x10^6$ viable MOPC-315 plasnacytoma cells, TS-CMI could be detected by day 5 and persisted through day 7 after grafting. By day 9, TS-CMI could not be demonstrated in vitro and the loss of TS-CMI persisted until death (14-18 days). In contrast, CMI to non-tumor antigens could be detected throughout the course of tumor growth when mice were simultaneously grafted with $1x10^6$ MOPC-315 tumor cells and immunized with either DNP-Ig or Mycobacteria.

It was further demonstrated that splenic RNA-rich extracts obtained from mice 5-7 days after tumor grafting could transfer TS-CMI to non-sensitized mouse cells in vitro and to "suppressed" cells obtained from mice 12-14 days after tumor grafting. On the other hand, RNA-rich extracts obtained from mice 12-14 days after tumor grafting were incapable of transferring TS-CMI to non-sensitized mouse cells. Our results suggest that: 1) TS-CMI develops early during the course of plasmacytoma tumor growth and is then lost or suppressed; 2) the loss or suppression of TS-CMI is specific for tumor antigens and does not affect non-tumor CMI; 3) TS-CMI to MOPC-315 plasmacytoma can be transferred to either normal or suppressed PEC in vitro with "immune RNA" extracts.

LEUKOENCEPHALOPATHY (LEP) IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA (ALL) RECEIVING PREVENTIVE CENTRAL NERVOUS SYSTEM (CNS) THERAPY – Rhomas Aur, Omar Hustu and Joseph Simone, St. Jude Children's Research Hospital

After identical remission induction therapy and preventive CNS therapy (2400 rads cranial plus 5 doses intrathecal methotrexate [MTX]), 260 children were randomized between Jan. '72 and Oct. '75 to maintenance therapy with: 1) MTX 40-80 mg/m^2 IV weekly; 2) MTX 20-30 mg/m^2 IV weekly with mercaptopurine daily; 3) as in 2 plus cyclophosphamide weekly; or 4) as in 3 plus cytosine arabinoside weekly. LEP developed in 9 of 20 patients in Group 1 after 10-50 wk (M-37) of continuous complete remission (CCR). All had received 50-80 mg/m^2 of MTX IV weekly. LEP was characterized mainly by drooling, dysarthria, dysphagia, ataxia, spasticity and seizure. Severity ranged from mild and self-limited to severe and debilitating; LEP was fatal in one child. LEP did not occur during CCR in Groups 2, 3, or 4. LEP occurred after 1-3 bouts of CNS leukemia in 2 additional patients in Group 1 and 11 of 240 patients in Groups 2, 3 and 4; all 13 received intrathecal MTX for treatment of the active CNS leukemia. Therefore, in this study of children with ALL given brain irradiation (2400 rads) and systemic chemotherapy, LEP developed only under two conditions: 1) after an average of 9 mo. of MTX 50-80 mg/m^2 IV weekly; 2) after 1 or more episodes of CNS leukemia.

INCREASED THERAPEUTIC ACTIVITY OF 9-β-D-ARABINOSYL-ADENINE (ARA-A) AGAINST LEUKEMIA P388 AND L1210 BY AN ADENOSINE DEAMINASE INHIBITOR – F.M. Schabel Jr., M.W. Trader, and W.R. Laster Jr., Southern Research Institute

Plunkett & Cohen (Cancer Res. 35:1547, 1975) reported increased therapeutic response of Ehrlich ascites with ara-A + an adenosine deaminase inhibitor (ADI) over ara-A alone. LePage et al. (Cancer Res., in press) have observed that ara-A, inactive vs L1210 or L1210/ara-C, is markedly active vs both when used in combination with 2'-deoxycoformycin (NSC–218321), an active ADI, on optimal schedules for S-phase-specific agents. We have independently observed marked therapeutic enhancement of ara-A by ADI vs P388, P388/ara-C, and L1210. Ara-A has limited activity vs P388 or P388/ara-C when used alone on qd, 1-9 days, treatment. Ara-A + ADI is curative at $\leq LD_{10}$ doses, qd, 1-9 days, in mice bearing $<10^6$ P388 cells. Ara-A used alone is essentially inactive at $\leq LD_{10}$ doses in mice bearing $<10^5$ L1210 cells on either qd, 1-9 days, or q3hx8, days 1, 5, & 9, schedule, similar to the activity of ara-C vs L1210. Thus, when deamination of ara-A was effectively blocked, it became more active vs a responsive tumor (P388) and markedly active vs an unresponsive tumor (L1210).

ANTILEUKEMIC ACTIVITY OF PSEUDOISOCYTIDINE (Ψ-ICR)– A NEW SYNTHETIC C-NUCLEOSIDE – J.H. Burchenal, K. Kalaher, T. O'Toole, R. Kiefner, C. Chu, K. Watanabe, I. Wempen, J.J. Fox, Memorial Sloan-Kettering Cancer Center

Because of the eventual development of resistance to arabinosylcytosine (ara-C) in patients with AML, a program has been designed by Fox et al. to synthesize C-nucleosides with antileukemic activity without cross resistance to ara-C and not susceptible to deamination. The first compound of this series is 5-ribosyl-isocytosine, a carbon isostere of 5-azacytidine. Ψ-ICR is active in vitro against the cells of ara-C sensitive and resistant mouse leukemias with ID50s ranging from 0.04 to 3.0 ug/ml. This effect can be blocked by cytidine (CR) 20 ug/ml but not by CdR or TdR. Up to 300 fold resistance to Ψ-ICR has been developed in vitro. These Ψ-ICR resistant lines show no cross resistance to ara-C, thioguanine or adriamycin. Ψ-ICR approximately doubles the survival time of mice with leukemias L1210, P815, L5178Y and AK44 and their ara-C, MP, MTX, and VCR resistant sublines. Ψ-ICR is not schedule dependant with 50mg/kg qdx10, 150 mg/kg q4dx3, or 225 mg/kg q4dx2 being equally active. It is also moderately active p.o. at 2-3x the i.p. dose. As with AzaCR, the toxicity and therapeutic effect of pseudoisocytidine are blocked by CR 50-100 mg/kg 15 minutes before but not 2, 8, or 24 hours later.

STUDIES ON THE POSSIBLE ROLE OF THE GLUCOCORTICOID RECEPTOR IN MODULATING THE LEVEL OF THE mRNA FOR TRYPTOPHAN OXYGENASE IN HEPATOMA AND HOST LIVER – P. Feigelson, L. Ramanarayanan & P. Colman, Columbia Univ.

Our previous studies indicated that hepatoma 7793 was devoid of, and host liver contained, the catalytic activity and the specific mRNA of tryptophan oxygenase (TO). Pretreatment of tumor-bearing rats with glucocorticoid four hours prior to sacrifice increased the TO catalytic activity and the mRNA for TO three-fold in the host livers but had no detectable inductive effect upon the tumors. Hepatoma cytosol was shown to contain a glucocorticoid receptor protein which was indistinguishable from its normal hepatic counterpart with respect to the binding of triamcinolone with high affinity and the ability of this steroid-receptor complex to undergo normal thermal activation enabling its binding to DNA-cellulose as well as to nuclei derived from host liver or hepatoma. Interchange experiments indicated no distinguishable differences in interactions between steroid-receptor complexes and nuclei derived from tumor or normal livers. Thus in both the absence and presence of inducing steroid, the lack of the gene product, i.e., the mRNA for TO, in the hepatomas is not due to the absence of hormone receptor nor to any detactable impairment of its ability to interact with normal or malignant nuclei.

MACROMOLECULAR ADDUCTS OF AFLATOXINS B_1 AND B_2 IN RAT LIVER IN VIVO – J.-K. Lin, D.H. Swenson, E.C. Miller, and J.A. Miller, Univ. of Wisconsin

The potent hepatocarcinogen aflatoxin B_1 (AFB_1) forms DNA and rRNA adducts in rat liver in vivo with 15-20 X the specific activity of the protein adducts. Acid hydrolysis of the nucleic acid adducts yields 2,3-dihydro-2,3-dihydroxy-AFB_1 (dihydrodiol) and indicates AFB_1-2,3-oxide is a major electrophilic precursor (Swenson et al., BBRC 60: 1036). High resolution liquid chromatography of acid hydrolysates of the nucleic acid adducts of AFB_1 yields several derivatives in addition to the dihydrodiol. One unidentified derivative is a precursor of the dihydrodiol. Aflatoxin B_2 (AFB_2) (2,3-dihydro-AFB_1) has low but discernible hepatocarcinogenicity ($<$1/115th that of AFB_1) in the rat (Wogan et al., Cancer Res. 31:1936). In rat liver in vivo AFB_2 gives 0.7-1.4% of the nucleic acid-binding and 35-70% of the protein-binding noted with AFB_1. The nucleic acid adducts obtained with AFB_2 yield the dihydrodiol and the other derivatives noted for AFB_1. From these data AFB_2 appears to be desaturated in vivo to yield low levels ($\sim$1%) of AFB_1. These findings support the concept that AFB_1-2,3-oxide is a reactive ultimate carcinogenic metabolite of AFB_1 and further indicate that alkylation of the nucleic acids is a critical reaction in carcinogenesis by AFB_1. These conclusions were also drawn from studies with the carcinogenic and mutagenic electrophile AFB_1-2,3-dichloride, a model for AFB_1-2,3-oxide (Swenson et al., Cancer Res. 35: 3811).

NCI ADVISORY GROUP, OTHER CANCER MEETINGS SCHEDULED FOR JUNE, JULY

National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis—June 2, NIH Bldg 31 Room 6, 9:30 a.m., open.

Diet, Nutrition & Cancer Program Scientific Review Committee—June 2-4, NIH Bldg 1 Wilson Hall, open 8:30–9:15 a.m. each day.

Cancer Control Intervention Programs Review Committee—June 3-4, NIH Bldg 31 Room 5, open June 3, 1–1:30 p.m., June 4, 8:30–9 a.m.

Committee on Cancer Immunotherapy—June 3, NIH Bldg 10 Room 4B14, open 1–1:30 p.m.

National Cancer Advisory Board Subcommittee on Centers—June 4, Westwood Bldg Room 825, 9 a.m.–5 p.m., open.

Carcinogenesis Program Scientific Review Committee A—June 4, Landow Bldg Room A809, open 9–9:30 a.m.

Committee on Cancer Immunodiagnosis—June 7-8, Landow Bldg Room C418, open June 7, 8:30–9 a.m., open June 8, 8:30 a.m.–adjournment.

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

Clinical Cancer Education Committee—June 9-10, NIH Bldg 31 Room 6, open June 9, 8:30-9:30 a.m.

Management of All Stages of Colo-Rectal Carcinoma—June 10, Roswell Park Continuing Education in Oncology.

Developmental Therapeutics Committee—June 10, NIH Bldg 31 Room 7, 9:30 a.m., open.

National Bladder Cancer Project Working Cadre—June 10-11, O'Hare Hilton, Chicago, open June 10, 8–10 p.m., open June 11, 8:30 a.m.–adjournment.

Cancer Special Programs Advisory Committee—June 10-12, NIH Bldg 31 Room 8, open June 10, 9–10 a.m.

Diet, Nutrition & Cancer Program Advisory Committee—June 11, NIH Bldg 1 Wilson Hall, 9 a.m., open.

Cancer Control Supportive Services Review Committee—June 11, NIH Bldg 31 Room 5, 8:30 a.m., open.

13th World Congress of Rehabilitation (including sessions on laryngectomies and mastectomies)—June 13-18, Tel Aviv.

Immunobiology Conference (sponsored by NCI Div. of Cancer Research Resources & Centers)—June 13-16, Hilton Head, S.C., all open.

Committee on Cancer Immunobiology—June 14, Hilton Head, S.C., open 1–1:30 p.m.

Virus Cancer Program Scientific Review Committee A—June 14-15, Landow Bldg Room C418, open June 14, 9–9:30 a.m.

Clinical Cooperative Group Chairmen—June 15, NIH (check with NCI for time and location).

Cancer Control Community Activities Review Committee—June 18, NIH Bldg 1 Wilson Hall, open 9 a.m.–3 p.m.

Cancer Control Supportive Services Grant Review Committee—June 18-19, NIH Bldg 31 Room 5, open June 18, 8:30–10 a.m.

National Medical Symposium—June 20-24, Univ. of Utah.

NCAB Subcommittee on Centers—June 20, NIH Bldg 31 Room 8, open 7:30–8:30 p.m.

NCAB Subcommittee on Planning—June 21, NIH Bldg 31 Room 11A10, 7:30 p.m., open.

National Cancer Advisory Board—June 21-22, NIH Bldg 31 Room 6, open June 21, 9–11:15 a.m., 1:30–5 p.m., open June 22, 9 a.m.–adjournment.

Cancer Control Intervention Programs Review Committee—June 24-25, NIH Bldg 1 Wilson Hall, open June 24, 8:30 a.m.–4 p.m., open June 25, 8:30 a.m.–2 p.m.

Joint Meeting of Virus Cancer Program Scientific Review Committees A & B—June 28-29, NIH Bldg 37 Room 1B04, open June 28, 9–9:30 a.m.

Cancer Control Grant Review Committee—June 28-29, NIH Bldg 31 Room 4, open June 28, 8:30–9:30 a.m.

Cancer Clinical Investigation Review Committee—June 28-30, NIH Bldg 31 Room 6, open June 28, 8:30–10 a.m., open June 29, 9 a.m.–noon.

National Prostatic Cancer Project Working Cadre—June 30–July 1, NIH Bldg 31 Room 4, open June 30, 8–8:30 a.m.

Third International Congress of Immunology—July 1-8, Sidney, Australia.

Meeting on Non-Specific Immune Stimulation in Experimental & Clinical Cancer Treatment—July 5-6, Bucharest.

Workshop on Computers in Radiotherapy in Europe—July 5-10, Vienna.

Combined Committees of Breast Cancer Task Force—July 7, Bethesda Holiday Inn, 8:30 a.m., open.

10th International Congress of Biochemistry—July 25-31, Hamburg.

International Assn. of Larengectomees Annual Meeting—July 27-31, Chicago.

SOLE SOURCE NEGOTIATIONS

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

Title: Oncology nursing programs in community hospitals
Contractor: Waterbury Hospital Health Center.

Title: Establishment of a gnotobiote originated rodent production colony
Contractor: Charles River Breeding Labs.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NO1-CP-65802-68

Title: *Optimal nutritional support as an adjunct to cancer therapy in the adult patient*
Deadline: *July 26*

This project will be multi-institutional cooperative effort dealing with the usefulness of supportive nutritional therapy, specifically intravenous hyperalimentation, for the adult cancer patient. The project will define the role of optimal nutrition in the therapy and management of the adult cancer patient. Objectives include determining 1) whether optimal nutritional support alters the rate of tumor growth; 2) whether optimal nutrtional support alters the status of the adult cancer patient such that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; 3) whether specific antineoplastic therapy interferes with the efficacy of nutritional therapy, impairs utilization or causes complications; and 4) how optimal nutritional support affects the host-tumor responses and host-immune response to cancer therapy.

Prospective offerors shall submit a separate business and technical proposal for each selected subject of the following tumor type/therapy modality segments: Offerors may submit proposals on any number of segments. 1) surgery—upper gastrointestinal tract 2) surgery—head and neck malignancies 3) radiotherapy—squamous cell carcinoma of the head and neck 4) radiotherapy—abdomen and pelvis malignancies undergoing high dosage treatment 5) chemotherapy—non-oat cell carcinoma of the lung 6) chemotherapy—testicular carcinoma 7) chemotherapy—carcinoma of the breast 8) chemotherapy—adenocarcinoma of the colon.

Each segment will involve 40 patients equally divided between control and optimal nutritional support treatments. Multiple awards are anticipated.
Contract Specialist: S.W. Ranta
Cause & Prevention
301-496-6361

CONTRACT AWARDS

Title: Systems analysis and information services resources for registries of human clinical protocols in cancer therapy
Contractor: Informatics Inc., $89,544.

Title: Study of antigen-binding receptors on T-cells
Contractor: Helsinki University, $28,800.

Title: Procurement of melanoma cell vaccine and in vitro assays for humoral and cellular cytotoxicity
Contractor: Litton Bionetics Inc., $320,607.

Title: Intrapleural BCG after primary surgery for lung cancer
Contractor: Albany Medical College, $65,774.

Title: Immune response of mice and rats to tumor associated antigens
Contractor: Litton Bionetics Inc., $191,680.

Title: Development and utilization of rehabilitation and/or continuing care resources and services
Contractor: Hospice Inc., New Haven, Conn., $532,924.

Title: Biochemistry of normal and tumor cell surface antigens
Contractor: Johns Hopkins Univ., $81,439.

Title: Cancer immunotherapy: Phase I study of efforts of immune stimulants on human immune response
Contractor: Sloan-Kettering Institute for Cancer Research, $136,164.

Title: Cell survace membrane components organization and dynamics
Contractor: Johns Hopkins Univ., $66,536.

Title: Circulating antigen-antibody complexes in cancer
Contractor: Univ. of Alabama, $86,265.

Title: Collect sera from high cancer risk populations
Contractor: Univ. of Minnesota, $84,500.

The Cancer Letter—*Editor* JERRY D. BOYD

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