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RESEARCH EDUCATION CONTROL

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P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

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ROGERS SUBCOMMITTEE REWRITES CANCER CONTROL DEFINITION, ADDS $45 MILLION OVER THREE YEARS

The House Health Subcommittee completed its work on the bill renewing the National Cancer Act this week and in the process redefined the Cancer Control Program and added $45 million in authorized funds for Cancer Control over the next three years.

The subcommittee, chaired by Paul Rogers (D.-Fla.), also added at the urging of Congressman Andrew Maguire (D.-N.J.) new provisions to the Act expanding NCI's role in prevention. One of these is almost

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In Brief

NEW CREG FOR SURGERY RESEARCH APPROVED; ONLY 30 BIOASSAY PROGRAM REPORTS STILL IN BACKLOG

"NEW APPROACHES to surgical oncology" is the title of a Cancer Research Emphasis Grant program to be offered later this year or early next year by NCI's Div. of Cancer Treatment. The DCT Board of Scientific Counselors approved the concept of the new CREG and suggested that up to $1 million be made available to support the five year awards. Board member Donald Morton initiated the action and offered as possible research areas the role of cyto reductive surgery in cancer management, development of more conservative surgery, standardization, and the roles of surgeons in hyperthermia, preoperative treatment and nutrition. More than half of all cancer patients are treated by surgeons, yet NCI now spends only $1.6 million a year on surgery research, Morton pointed out. . . . **HOW GOES** the Bioassay Program backlog? NCI Director Arthur Upton said last week that 44 reports have been published, 83 are finished in final form and are awaiting publication, 118 are in the process of being printed, and 187 have been drafted and are in final analysis. This leaves only 30 still in the backlog. . . . **LEUKEMIA OUTBREAK** in Rutherford, N.J., in which six children attending one school were stricken, "is a statistical phenomenon that happens all the time," NCI Deputy Director Guy Newell told the President's Cancer Panel. Rutherford is not the only place where clusters of leukemia and lymphoma have developed, Newell said. The HEW Center for Disease Control investigates all such incidents, including Rutherford. "It's bound to occur by chance alone. In all the cases CDC has worked up, there never has been any linkage," Newell said. . . . **INTERNATIONAL ENDOCURIETHERAPY** symposium, sponsored by the USC Cancer Center Radiation Medicine Unit, is scheduled for June 30-July 2 at the Los Angeles Bonaventure Hotel. Contact Frederick George III, USC School of Medicine, 2025 Zonal Ave., L.A. 90033, phone 213-226-5031. . . . **NEW PUBLICATION**: "Immunotherapy of Cancer: Present Status of Trials in Man," edited by William Terry of NCI and Dorothy Windhorst of Hoffmann-La Roche. Raven Press, $49.50.

MAGUIRE AMENDMENT WOULD PUSH NCI INTO CONFRONTATIONS WITH REGULATORS

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certain to embroil NCI in controversies with the regulatory agencies if it is vigorously carried out.

The bill (H.R. 10908) now goes to the full House Commerce Committee, where it is doubtful any significant changes will be made. Further amendments could be offered when it reaches the House floor, later this spring or in the summer.

Redefinition of cancer control probably will not lead to any major changes in programs supported by the Div. of Cancer Control & Rehabilitation, although it could help stimulate some new initiatives.

The new provision on cancer control states:

"The director (of NCI) shall establish and support demonstration, education and other programs for the detection, diagnosis, prevention and treatment of cancer and for rehabilitation and counseling respecting cancer."

That amendment was put in by Rogers. Maguire succeeded in adding:

"Programs under this section shall include demonstration and education on effective methods for early detection of cancer and the identification of individuals with a high risk of developing cancer; improved methods of patient referral to appropriate centers for early diagnosis and treatment of cancer; demonstration of new methods for the dissemination of information to the general public concerning the early detection and treatment of cancer and information concerning unapproved and ineffective methods, drugs and devices for the diagnosis, prevention, treatment and control of cancer."

That last provision appears to be an invitation to NCI's Div. of Cancer Control & Rehabilitation, and perhaps Office of Cancer Communications, to take an active role against laetrile and other quackery.

Congressman Tim Lee Carter (R.-Ky.) succeeded in adding this provision to the control redefinition:

"Programs established under this subsection shall include locally initiated education and demonstration programs (and regional networks of such programs) to transmit research results and to disseminate information respecting the detection, diagnosis, prevention and treatment of cancer and counseling respective to cancer to physicians and other health professionals who provide care to individuals who have cancer."

Carter's amendment was the result of some more effective lobbying by David Goldenberg, executive director of the Ephraim McDowell Community Cancer Network in Kentucky (see story elsewhere in this issue).

Rogers' original bill had authorized $86 million for cancer control in the 1979 fiscal year, $88 million in 1980 and $90 million in 1981. The subcommittee added $10 million for 1979, $15 million for 1980 and $20 million for 1981. The levels for other NCI activities remain at the original figures submitted by Rogers—$924 million, $927 million, and $930 million.

Whether the additional funds carries any weight with the appropriations committees remains to be seen. The President's budget asks only $64 million for control in 1979.

Maguire was successful in getting Rogers and the subcommittee to accept a provision from a bill he had introduced which in effect will get NCI more deeply involved in the regulatory process. This provision requires NCI to annually publish a list of known or suspected carcinogens to which a significant number of persons in the U.S. are exposed. The report will include information on the nature of such exposure and an estimate of the number of persons exposed.

The Maguire amendment then adds, in language certain to lead to confrontations with bureaucrats at FDA, EPA and the other regulators:

The report will include an "evaluation of the effectiveness of existing regulatory standards designed to reduce or eliminate exposure to carcinogens, and recommendations of respective ways in which such standards could be improved."

What this means is that the NCI director will be telling the FDA commissioner, the EPA administrator, and the OSHA director—all of whom outrank him in the federal hierarchy—what they should be doing to get carcinogens out of the environment.

Maguire's intent is clear: Get NCI's scientific prestige involved in pushing the regulatory agencies into faster and more effective action on carcinogens, and to help generate public pressures on the agencies.

Most of the other items in the Rogers bill are not controversial, and there were few additional changes to the bill as he had introduced it.

In what NCI executives considered was a major victory, Rogers agreed to include the addition of basic research as an activity that can be supported by NCI in cancer centers. Basic research at centers has been conducted under a provision of the Public Health Service Act which authorizes basic research support for NIH in general. Gaining that authorization under the Cancer Act provides NCI with some additional flexibility. One drawback: The Cancer Act limits those grants to three years; NCI had hoped to extend authorization to five.

Rogers added an amendment under centers authorization, adding continuing education for health professionals and allied health professions, and public education. It had been more or less assumed these activities could be supported by NCI, but this clarifies the intent of Congress.

The new bill requires the President's Cancer Panel to meet only four times a year instead of monthly. Panel members generally attend the four meetings a

year of the National Cancer Advisory Board, so this is not a downgrading of the Panel in any way.

The bill does downgrade the appointment of the NCI director and NCAB members, from the President to the HEW secretary. Former Presidents Nixon and Ford kept those appointments in the White House, but President Carter has delegated them to Secretary Califano anyway, so there is no substantive change.

The Rogers bill adds as ex officio members of NCAB the heads of NIOSH, FDA, EPA, Consumer Product Safety Commission, National Institute of Environmental Health Sciences, and the Secretary of Labor. These plus the existing ex officio members –representatives of the Veterans Administration, Dept. of Defense, White House Office of Science & Technology, NIH director and HEW secretary– specifically will not have a vote in Board actions (that previously has been unclear).

One significant amendment put in by Rogers:

All of NIH will be authorized to conduct and support through grants and contracts studies of substances for their carcinogenic, teratogenic, mutagenic, and other harmful effects. Such studies will be conducted at the request of other agencies, provided those agencies pay for them.

That amendment would seem to give congressional approval, although it is not really needed, for HEW to set up either at NCI or more likely at NIEHS a program to combine all toxicity testing, including NCI's Bioassay Program. HEW is still pondering the disposition of the NCI carcinogenesis testing effort, a decision that is tied in with the institute's reorganization.

The Rogers bill specifically permits distribution of test chemicals, living organisms and research animals to grantees and others, in addition to contractors when they "are in short supply or uniformity will significantly improve research results." This authority is extended to all of NIH, but it will apply mainly to NCI and its repository of reference chemicals.

The bill authorizes NIH to hire expert consultants in addition to authorized personnel ceilings. Rogers originally had asked for a number set at 2.5% of all permanent full time employees, but the subcommittee increased that to 4%, or from 240 to 320 positions. These will be in addition to the 151 authorized for NCI.

Finally, the bill removes what has become to many an obnoxious symbol of hypocracy in the law: The provision in the PHS Act requiring the government to provide tobacco products free to patients in PHS hospitals.

KENTUCKY ESTABLISHES STATE CANCER COMMISSION WITH $1 MILLION BUDGET

The Kentucky legislature has approved and Gov. Julian Carroll has signed a bill to establish a 13-member state Cancer Commission charged with strengthening and implementing cancer programs, including multiphasic screening clinics, public education, a central tumor registry and research to improve cancer detection, diagnosis and therapy. The bill gives the commission an annual budget of $1 million and authority to support the construction of a cancer center affiliated with one or both university medical centers in the state.

David Goldenberg, executive director of the Ephraim McDowell Community Cancer Network headquartered in Lexington, said, "The passage of this legislation represents a milestone in the state's effort to control cancer, whose mortality rate in Kentucky is higher than the national average. The state commitment to controlling cancer is one of the results of the National Cancer Act and the National Cancer Institute's support of cancer center planning and cancer control programs in Kentucky. Kentucky represents a special problem in cancer control, since it is part of the Appalachian chain containing vast pockets of poverty and poor educational and health care resources."

Goldenberg and his McDowell Network colleagues were instrumental in pushing the bill through the legislature. William Kenton, speaker of the House of Representatives and author of the bill, said, "This new cancer act could become a model for the nation and will help bring Kentucky to the forefront of cancer care and research. I am hopeful that the funds of the Kentucky Cancer Commission will help expand the initial strivings of the McDowell Network in its efforts to dispel an attitude of hopelessness associated with cancer, and through its education and early detection efforts render a larger percentage of cancers in Kentucky controllable or preventable."

The McDowell network was started at the Univ. of Kentucky Medical Center under a cancer center planning grant. Peter Bosomworth, vice president of the medical center, and Ward Griffen Jr., chairman of surgery, and Goldenberg, director of experimental pathology, were the principals. The network has its own board of directors consisting of professional and lay citizens from around the state. It emphasizes community based and community directed cancer education and control activities.

The university relinquished its cancer center responsibilities to the network but remained as one of its divisions. Ben Roach, chairman of the McDowell board and a family practitioner, said, "This arrangement is consistent with the Univ. of Kentucky's mission as a state university, and mitigates the usual community animosity to ivory tower programs."

PINKEL CORRECTS REPORT ON TREATMENT OF ALL – TWO DRUGS ARE BETTER THAN ONE

Donald Pinkel, chairman of the Dept. of Pediatrics at the Medical College of Wisconsin, was quoted incorrectly in ***The Cancer Letter*** (April 7) report on his Karnofsky lecture at the American Society of

Clinical Oncology meeting. The report said that studies cited by Pinkel had found that the addition of second, third and fourth drugs in treating acute lymphocytic leukemia produced no better results than single drug therapy.

"In the Karnofsky lecture at ASCO I indicated that in our St. Jude Study VIII the patients receiving two drugs (mercaptopurine and methotrexate) had better remission experience than those receiving one drug (methotrexate alone)," Pinkel wrote. "However, the addition of a third (cyclophosphamide) and of third and fourth drugs (cyclophosphamide and arabinosyl cytosine) did not improve remission duration or the frequency of lengthy remission. Thus, two drugs are superior but not three or four drugs. Morbidity was least for the two drug group."

Pinkel also felt that another item in ***The Cancer Letter*** report "is open to misinterpretation." Referring to his statement concerning the prospect that 50% of ALL patients can be cured, the report said, "The half who are being cured are those who receive the optimal treatment in the most advanced facilities." Pinkel was quoted as saying, "Most children with the disease around the world do not benefit from these advances. The treatment is too complex and is not accessible to them."

To correct any misinterpretation, Pinkel wrote, "One-half of those who receive optimal treatment are apparently being cured, but worldwide the vast majority of children do not receive optimal treatment so that the worldwide apparent cure rate is much lower."

NIH ATTEMPTING TO DEFINE "PREVENTION" AND ITS ROLE IN TECHNOLOGY TRANSFER

NIH and NCI have been caught up in "a flurry of efforts" related to increasing the emphasis on disease prevention, Director Arthur Upton told the President's Cancer Panel last week. One of the results: Upton has been named chairman of an NIH working group charged with defining prevention in the context of NIH's mission.

Upton said prevention is being considered in two classifications, primary—prevention of the process leading to biological onset of disease—and secondary—prevention of progression of disease once the biological process has started.

"The mission of NIH is predominantly research, and it is not clear how to handle an attempt to inventory research in prevention," Upton said. Two concepts have emerged. First, the etiology and pathogenesis of any disease involves a long sequence of reactions, beginning with inherited determinants, followed by successions of interactions between environmental stimuli and inherited genetic factors. Somewhere along the pathway, we envisage prevention—through genetic counseling before birth, perhaps utilizing amniocentesis, or early in life, identifying other factors, until disease appears. After disease starts, we must identify means to prevent further progression."

All these activities require basic research, to increase understanding of the biological problems which would provide the basis for applied research, to solve the problems. At that point, the next step would be transfer of the technology, Upton said.

Panel member Paul Marks asked about the relation of the new NIH Office of Medical Application of Research, headed by former NCI Div. of Cancer Treatment deputy director Seymour Perry, to NCI's cancer control activities.

NCI assistant director Bayard Morrison commented that OMAR "is still trying to get its bearings," and is in the process of trying to get each institute to formulate its technology transfer activities. Chairman Benno Schmidt pointed out that a bill by Sen. Edward Kennedy would create a National Institute of Technology Transfer.

Div. of Cancer Control & Rehabilitation Director Diane Fink said her division does have the job of technology transfer, as far as NCI is concerned. The new institute, with authority to establish demonstration programs, "would be not unlike NCI was several years ago when we got started with cancer control."

"It is not the feeling across the country that the highest priority of our cancer control effort is technology transfer," Marks said. "We have the opportunity here to sharpen it up. It might be appropriate to develop some sort of policy statement."

"I agree that we are on the threshold of something important," Fink said. "What is the medical profession doing with our research?"

"I have a different slant on this," Schmidt said. "There is a tendency to make technology transfer seem easier than it is. That if only someone would get with it, a long list of good things would happen. I don't believe it.

"There are two sides," Schmidt continued. "One is that there is a lot of good science on the shelf that is not being used, and that scientists are not interested in getting it out. There may be some in that category, and I think the reasons for it not getting out are explainable without the benefit of hindsight.

"Another side is that some science gets out too early. There may be some of that, and with hindsight it now looks as if it got out too soon. I think the balance between those sides is probably a pretty good one. If you tried to make a firm policy to cover those things, it probably would keep a lot of good things from happening.

"Most technology transfer probably does not take place because Washington, or NIH, or the Cancer Institute, decided it should. Most technology transfer takes place in the most enlightened medical environment, in the private sector where there is a combination of knowledge of what basic science is going on and the clinical genius exists with knowledgeable people trying every day to put those things together.

"The idea that there is a lot more technology transfer to be done is an idea for which I have not heard a good case. It is a disservice to Congress to indicate there is.

"On the Control Division itself, there are as many definitions of what the divisions should do as there are people offering to define it."

Schmidt has begun to lose patience with critics who demand that NCI spend more money on prevention.

"If we could spend $50 million, $100 million, $500 million more on prevention, how would we spend it?" he asked. "The only way to test if we are spending enough is to decide how we would spend additional money, and then look at the priorities."

Upton said the National Heart, Lung & Blood Institute, the only other NIH institute with a control mandate, is looking at the Smoking & Health Program it supports jointly (but to a lesser degree) with NCI. "We're going to look carefully at that program," Upton said.

Schmidt said he thought another question that should be considered is whether the Clinical Cooperative Groups, now part of the Div. of Cancer Treatment, should be part of the control program. "They are exactly what one of the programs the control division would be doing if it were not already being done. It always struck me the cooperative groups were the nearest overall approximation of what Congress thought it was talking about when it wrote control into the Act."

Upton agreed that might be the case except that control is generally limited to education and demonstration and does not include clinical trials. "I see control as demonstration, after the technology is evaluated."

DCT Director Vincent DeVita noted that DCCR does put some money into the cooperative groups, supporting the effort to involve more community hospitals in the groups' clinical trials. This is an example of the control function, in upgrading oncology in community settings, DeVita said.

NCCP LANDS $1.7 MILLION CONTROL GRANT, NEEDS SOMEONE TO HELP ADMINISTER IT

The Northern California Cancer Program, which has just received a $1.7 million three year cancer control grant from NCI, is looking for an associate director for cancer control to implement that effort.

NCCP's cancer control program will "emphasize the translation and application of basic and clinical research findings into practical programs of patient care, public and professional education and community outreach," the organization said in its announcement seeking applicants for the position. "The candidate must possess either an MD or PhD with research standing desirable."

Salary will be $45-50,000 plus fringes. Resumes should be directed to Stephen Carter, director, or John Richey, administrator, P.O. Box 10144, Palo Alto, 94303.

Carter said the award, from NCI's Div. of Cancer Control & Rehabilitation, will be used to support programs planned by NCCP in cooperation with the California Dept. of Health, West Coast Cancer Foundation, Northern California Oncology Group, Coalition for the Medical Rights of Women and several regional cancer organizations. The programs range from development of data bases and epidemiological studies to a public education effort by a community based group.

"We serve such a vast area (Northern California and Northwestern Nevada) that we've divided ourselves into integrated service areas," Carter said. "Each ISA observes natural geographic boundaries and patient flow patterns and is usually centered about a major city. Working with the ISAs, we hope to help each area identify its own cancer resources and needs and develop effective responses to those needs."

The grant will enable NCCP to further develop four ISAs through other regional groups—Sacramento-Sierra through the Greater Sacramento Cancer Council; North Counties through the West Coast Cancer Foundation; San Jose through the Greater San Jose Cancer Council and the Institute for Medical Research; and East Bay through the East Bay Cancer Program and the Bay Area Tumor Institute.

ISAs are being developed by NCCP independent of the cancer control grant with the Central California Cancer Council in Fresno and the Northern Nevada Cancer Council in Reno.

Funds from the cancer control grant will be used to help support the following additional programs:

—The outreach program of the Northern California Oncology Group, the cooperative clinical trials arm of NCCP, will be developed with the ISAs. This program calls for the participation of community physicians in research activities and the rapid transfer of recent clinical findings to community physicians and their patients.

—The California Tumor Registry of the state Dept. of Health and NCCP will oversee a coordinated program of cancer data collection and management, systems development and information dispersal. Technical assistance will be provided to many community based institutions in program planning, design and evaluation; data collection and management; and in the development of tumor registries and both epidemiological and statistical studies.

—The Coalition for the Medical Rights of Women is being funded through NCCP for a consumer information network concerning diethylstilbesterol. DES was a drug prescribed to many pregnant women starting in the 1940's and has since been linked to cancer and other possible disorders in DES exposed offspring. The program planned by the Coalition includes identification of DES mothers and their

children, establishment of referral sources and follow-up, and the development of training programs for health professionals and consumer groups. A unique aspect of this program is the inclusion of consumers in every stage of planning, implementation and evaluation.

CONTRACT AWARDS

Title: Study of mortality experience of children inoculated with SV40 virus in early life, continuation
Contractor: Case Western Univ., $40,959.

Title: Development of group testing procedures for screening carcinogens, continuation
Contractor: UCLA, $50,000.

Title: Incorporation of six alteration/renovation projects as necessary for the performance of the cancer research program being conducted at the Frederick Cancer Research Center, modification
Contractor: Litton Bionetics, $355,732.

Title: Chemoimmunotherapy of actue myelocytic leukemia
Contractor: Mount Sinai School of Medicine, $139,621.

Title: Support services for molecular studies of cancer, continuation
Contractor: Meloy Laboratories, $481,690.

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-CM-87229

Title: *Establishment and operation of rodent production centers for inbred, hybrid, and outbred rodents*
Deadline: *Approximately June 16*

Under maximum barrier and modified conventional environmental conditions, as (1) progenitors for large-scale production colonies and (2) for laboratory investigations sponsored by the Div. of Cancer Treatment, NCI. To be considered for award of a contract, respondents must meet the following criteria:

1. Contractor(s) must be accredited breeders with the Drug Development Program, DCT, and must have, for the maximum barrier facility type award, an existing barrier facility with, as a minimum, an absolute filtration system, mechanical cage washing machines, auxilliary power sources, autoclaves (steam sterilizers) with sufficient capacity for large numbers of caging equipment, and large volumes of animal food and bedding.

2. Contractors must have a minimum of two years experience in the production of inbred and/or hybrid and/or outbred laboratory rodents. This experience shall be based upon the production and sale of a minimum of 1500 rodents per week. A total of eight tasks is anticipated which will include cage levels of 4,000, 4,500, 7,000 and 8,000 cages. One task will include the requirement of a modified conventional facility. Another task will include the requirement of physical location so that truck delivery is available to NIH, Bethesda. Still another task will include a requirement of access to an international airport which can expedite shipments to Philippines Islands, Japan and other Far Eastern areas, and to Western European areas.

It is anticipated that multiple awards will be made as a result of this RFP. It is also anticipated that awards will be for a three-year incrementally funded period of performance.

Contract Specialist: D. Abbott
Cancer Treatment
301-427-8125

RFP NO1-CP-85627-72

Title: *Attitudes and behavior of cancer patients with respect to diet, nutrition, and food consumption: Implications for intervention protocols and educational materials*
Deadline: *June 19*

The primary objective of this study is to provide information on the attitudes and behavior of cancer patients with respect to diet, nutrition, and food consumption. A survey will be conducted to provide information on these relationships and will include nutritional, dietary, attitudinal, behavioral, metabolic, and physiologic components. Psychological, anthropological, and traditional methods and techniques will be used to gather these data.

Collected data will be evaluated to develop hypotheses on the effect of attitudes and behavior on food consumption, and to provide information for the development of educational and informational materials. These materials will be directed to two target audiences: health care professionals and the families of cancer patients. These materials will serve as a mechanism for describing the role of attitudes and behavioral patterns of cancer patients relative to dietary and nutrient intake.

When possible, known techniques and procedures will be described which may be used to modify atti-

tudes and behavior patterns which may consequently increase food intake, thereby minimizing malnutrition and improving the overall quality of life. In the proposal, the offeror will include a tentative project schedule showing the time required to conduct the survey, the summarization and evaluation of the results, and the development of the educational and informational materials. Proposers must document the availability of cancer patient populations with admission records from the past three years. Access to patients and their medical records through hospital and primary care physician concurrence must be demonstrated in the proposal.

Contract Specialist: Jackie Matthews
Carcinogenesis
301-427-7574

ABSTRACTS OF OUTSTANDING PAPERS PRESENTED AT ANNUAL ASCO MEETING

Following are the remaining abstracts of papers selected by the program committee as among the outstanding at the recent meeting of the American Society of Clinical Oncology. The others appeared in the last two issues of ***The Cancer Letter.***

THE USE OF CRYOPRESERVED AUTOLOGOUS BONE MARROW FOLLOWING MARROW-LETHAL CHEMORADIOTHERAPY IN THE TREATMENT OF SELECTED PEDIATRIC MALIGNANCIES — Herbert Kaizer, Brigid Leventhal, George Santos, Gerald Elfenbein, Michael Weiner and Moody Wharam, Johns Hopkins Oncology Center

Three children with advanced stage, bone marrow negative, Burkitt's lymphoma, neuroblastoma and rhabdomyosarcoma did not achieve complete remission status with conventional chemotherapy. Under general anesthesia, bone marrow was aspirated from each patient (1 to 4 x 10^8 nucleated cells/kg) and cryopreserved. An in-vitro colony forming assay in a semi-solid suspension tissue culture system (CFUc) indicated that the marrow contained a normal quantity of hematologic progenitor cells before preservation. After thawing, approximately 50% of the CFUc present in the fresh marrow was recovered. Treatment consisted of radiation therapy to known sites of disease followed by intensive combination chemotherapy with adriamycin and cyclophosphamide, a marrow-lethal dose of total body radiation, and then autologous bone marrow infusion. Each patient has had reconsitution of the immune system and all hematopoietic cell lines. Significant tumor response has been observed in each patient and the child with Burkitt's lymphoma has been disease-free for nine months.

Conclusions: 1) Autologous bone marrow infusion permits hematologic reconstitution following marrow-ablative therapy. 2) A quantity of marrow sufficient for this purpose remains viable following cryopreservation even when obtained from patients previously exposed to chemotherapy. (This procedure is currently being applied to patients with initial bone marrow involvement who, following conventional chemotherapy, have a tumor-free marrow.) 3) The intensive therapeutic regimen described carries acceptable toxicity and promises an improved probability of long-term control for selected, advanced pediatric malignancies.

THERAPY OF UNFAVORABLE HISTOLOGY NON-HODGKIN'S LYMPHOMA (NHL) WITH HIGH DOSE METHOTREXATE AND CITROVORUM FACTOR RESCUE (MTX/CF), BLEOMYCIN (B), ADRIAMYCIN (A), CYCLOPHOSPHAMIDE (C), ONCOVIN^R (O), AND DECADRON (D) (M-BACOD) — Arthur Skarin, George Canellos, David Rosenthal, William Moloney and Emil Frei III, Sidney Farber Cancer Institute, Peter Bent Brigham Hospital and Harvard Medical School

Although intensive combination chemotherapy programs have improved the prognosis of unfavorable histology NHL, namely diffuse undifferentiated (DU), diffuse histiocytic (DH) and diffuse poorly differentiated lymphocytic (DPDL), a significant number of patients do not achieve complete remission (CR), and early relapse including CNS involvement occurs in about 20% of patients. MTX/CF is active in NHL, is non-myelosuppressive, and is effective in established CNS lymphoma. Thirty-four patients (pts) with advanced unfavorable histology NHL 8 stage III, 26 stage IV) received MTX/CF (3 Gm/m^2 i.v. q 3 wks) cycled between B (4 mg/m^2 i.v., A (45 mg/m^2 i.v.), C (600 mg/m^2 i.v.), O (1 mg/m^2 i.v.) and D (6 mg/m^2 p.o. qd x 5) q 3 wks x 10. Twenty-five pts are evaluable (9 recently entered). Of 19 pts with DH or DU, 16 (84%) achieved CR, with a median duration of 5+ mon. and median survival of 9+ mon., 2 had a partial response (PR) and 1 no response. Of 6 pts with DPDL, 3 (50%) had a CR (median duration 14+ mon. with median survival 16+ mon.) while 3 had a PR. Reversible myelosuppression related to C and A occurred in the majority of pts with a median WBC of 1700/mm^3 which was not significantly affected by MTX/CF. Reversible increase in creatinine occurred in only 3% of courses. No drug related deaths occurred. One pt developed fatal CNS involvement. M-BACOD has acceptable toxicity, results in an impressive CR rate in DH and DU unfavorable histology, and may reduce the incidence of CNS lymphoma.

The following abstracts are from papers presented at the session on phase I and II trials. Although not on the program committee's list, they are reprinted here as examples of new chemotherapy now being evaluated which may soon by ready for more extensive clinical use.

CHLOROZOTOCIN: PHASE I TRIAL OF THE 5-DAY SCHEDULE — Tom Anderson, Richard Fisher, Audrey Barlock, Robert Young, NCI

Chlorozotocin (NSC 178248) is a water-soluble nitrosourea analogue of BCNU which has significant antitumor activity in L1210 leukemia while exhibiting relative bone marrow sparing effects. The regimen utilized in this Phase I study in the I.V. treatment x 5 days every 6 weeks. Twenty-two patients (pts) with solid tumors have been studied (melanoma-7, breast-6, ovary-5, sarcoma, islet cell, hepatoma, undifferentiated carcinoma). Twenty had become refractory to extensive previous chemotherapy and/or radiotherapy. Pts were entered at 1.25, 7.5, 15, 20, and 30mg/M^2 day x 5 days. No pts had their dose escalatedso that potential cumulative bone marrow toxicity could be identified. No toxicity was observed at doses less than or equal to 20 mg/M^2/day x 5. At 30 mg/M^2/day x 5 hepatocellular toxocity was produced in 1/17 pts. Delayed (3-4-wks) bone marrow suppression was observed; thrombocytopenia in 3/7 pts (one life-threatening), leukopenia in 1/7 pts. No cumulative bone marrow toxicity has been observed to date although no pt. has recieved more than 4 cycles of therapy. Unlike the single dose trial, nausea and vomiting were not observed at comparable tota l doses utilizing the 5-day schedule. One pt with ovarian cancer had disease stabilization.

In mice, chlorozotocin has been shown to be cytotoxic to T- and B-lymphocytes, and to reduce the ability of residual T-cells to proliferate in response to non-specific mitogens. Preliminary studies indicate that some pts may also exhibit suppression of T-cell function after treatment with chlorozotocin. Because of its lack of gastrointestinal toxicity and apparently modified bone marrow activity, the 5-day schedule of chlorozotocin, at doses less than or equal to 30mg/M^2/day x 5 (less than or equal to 150 mg) should be tested in that spectrum of tumors responsive to other nitrosoureas to evaluate its relative therapeutic efficacy.

A PHASE I STUDY OF CHLOROZOTOCIN (NSC 178248) — John Kovach, Charles Moertel, Allan Schutt, Michael O'Connell, Mayo Clinic

Chlorozotocin, a nutrosourea with less carbamoylating activity and purposely less hematologic toxicity than other nitrosoureas was administered to advanced cancer pts by IV push either daily for 5 days or one day only every 6 wks. Total dosages studies on the 5 day schedule ranged from 12.5 to 200 mg/m^2 (39 courses in 23 pts). Dosages of 150

and 200 mg/m^2 were studied on the single day schedule in 6 pts each. Limiting toxicities were thrombocytopenia and leukopenia. On the 5 day schedule, thrombocytopenia (less than 150 x 10^3 cells/mm^3 occurred in 2/7 courses at a total dose of 37.5 mg/m^2 (81,54), 0/4 courses at 100 mg/m^2, 3/9 courses at 150 mg/m^2 (135,82,80), and 4/6 courses at 200 mg/m^2 (120,67,15,135). The median day nadir of thrombocytopenia was 28 (range 12-38) and median day recovery, 40 (range 18-43). Leukopenia (less than 4000 cells/mm^3) occurred in 1/3 courses at 12.5 mg/m^2 (3,6), 0/7 courses at 37.5 mg/m^2, 0/4 courses at 100 mg/m^2, 4/9 courses at 150 mg/m^2 (range 2.6-3.8) and 5/6 courses at 200 mg/m^2 (range 1.4-3.8). The median day nadir of leukopenia was 42 (range 23-54) and median day recovery, 57 (range 24-67). Dosages of 150 and 200 mg/m^2 on the single day schedule appear to cause greater hematologic toxocity than the same total dosages given over 5 days. Gastrointestinal toxicity was mild, nausea occurring in 9/51 and vomiting in 6/51 courses without clear-cut relationship to dosage. Minor, reversible, non-dose related increases in SGOT occurred at all dosages on both schedules. No renal or CNS toxicities were noted. The plasma T½ of intact N-nitroso groups averaged 9 min. (8 courses) after doses at or less than 40 mg/m^2 and 12 min. after doses of 150 or 200 mg/m^2 (10 courses). One pt with large cell carcinoma of the lung and one with melanoma and renal cell carcinoma had objective responses in nodal metastases.

PHASE II STUDY OF CHLOROZOTOCIN – Daniel Hoth, Thomas Butler, Stanley Winokur, Arthur Kales, Paul Woolley, and Philip Schein, Lombardi Cancer Research Center

The phase I investigation of chlorozotocin, a new chloroethyl nitrosourea, demonstrated that platelet depression was the dose-limiting toxicity in patients receiving single doses of greater than 120 mg/m^2 (Proc. ASCO 18:309, 1977).

Fifty evaluable patients with advanced measurable malignancies have been treated in an ongoing phase II trial utilizing doses of 120 mg/m^2 I.V. Q6weeks. A total of 11 objective partial responses have been recorded. These include: 4/11 with melanoma (responses observed in subcutaneous nodules in all 4), 2/14 with colon cancer (1 pulmonary, 1 hepatic lesion), 1/5 with adenocarcinoma of the lung (subcutaneous nodule), 1/1 with breast cancer (hepatic lesion), 1/1 nodular poorly differentiated lymphoma (hepatomegaly), 1/1 CCL (lymphadenopathy). One adult with acute lymphoblastic leukemia experienced a decrease in bone marrow blasts from 90% to 25%. The median duration of response for all patients was 3+ weeks (range, 2-12 weeks). None of these responses were associates with significant myelotoxicity (WBC less than 4,000/mm^3 or platelets less than 100,000/mm^3). However, 4 nonresponding patients treated at the 120 mg/m^2 dose level experienced platelet nadirs of less than 20,000/mm^3, and required platelet transfusion. All had been previously treated with 5-FU, adriamycin and mitomycin-C (FAM). As in our phase I study, significant platelet or WBC depression was not found at this dose level in any patient who had not received prior therapy. No cumulative toxicity has been observed to date. Based on these preliminary data, continued phase II study of chlorozotocin is indicated.

PHASE I TRIAL–MISONIDAZOLE (RO-07-0582)–A NEW RADIOSENSITIZER – Todd Wasserman, Richard Johnson, Gilbert Lawrence, Charles Gomer, Wolfgang Sadee and Theodore Phillips, Univ. of California (San Francisco) and Roswell Park Memorial Institute

The radiosensitizer misonidazole is in a phase I clinical trial in the Radiation Therapy Oncology Group (RTOG). This study opened in July 1977 and has accessioned 18 cases to date. All patients have advanced cancer, but normal renal and hepatic function. The drug (an enteric coated 0.5 gm tablet) is given on the dose schedule of a single oral dose weekly for 3 or 6 wks in separate patient groups. Radiation therapy is given 4-6 hrs after drug administration to allow for maximal serum and tumor levels. The initial dose level was escalated by 1 gm/m^2 increments, and is currently 3 gm/m^2. The pharmacologic evaluation includes measurement of blood and urine drug levels of both misonidazole and its principle demethylated metabolite, Ro-05-9963, using high pressure liquid chromatography (HPLC) and U.V. spectrophotometry. The HPLC assay has proven to be more sensitive. Peak serum levels occur between 1-3 hours after drug ingestion. Serum half lives are 10-24 hours. Urinary excretion is primarily of the metabolite, while the blood contains primarily misonidazole. Currently toxicity has only involved mild to moderate nausea and vomiting and one case of sensory neuropathy (total dose 15 gm).

CLINICAL ACTIVITY OF A NEW ANTHRACYCLIN DERIVATIVE IN MALIGNANT DISEASES – C.I. Jacquillat, M. Weil, M-F Auclerc, R. Maral, V. Izrael, J. Bernard, Hopital Saint-Louis, Paris, France

Among the anthracyclin a semi-synthetic derivative, the 33 921 R.P. (R=$-CH_2-O-CO-CH(OC_2H_5)2$) seems especially encouraging. Eighty-three patients (pts) were given this drug but doses and schedules varied according to diseases and to time. 23 pts with advanced acute leukemia (A.L.) were given 5 to 7 sequential (seq.) doses of 2 mg/kg/-day. We observed 9 C.R. in 14 A.L.L. and 1 C.R. in 9 A.M.L. Besides aplasia, the most striking toxicity (t.) consisted in oral and pharyngeal mucositis and severe diarrheas. Other pts were given intermittent schedules 1 or 2 seq. doses of 2 mg/kg. In 7 advanced disseminated non Hodkgin lymphoma of unfavorable histology, remissions were observed in 6 pts. Shrinkage of skin involvements was observed in 3 pts. The maximum dose was 14 mg/kg in 2 months. With this schedule hematological and mucosal t. were minor in 4 pts and absent in 3 pts. In 4 mycosis fungoides treated with 1 mg/kg/w. 4 partial remissions were observed with impressive remission of skin lesions and less results on lymphnodes. Decrease of a skin lesion was observed in a metastatic renal carcinoma. Duration of remission cannot be estimated yet. No cardiac toxicity was encountered but the total dose did not exceed 15 mg/kg. This drug has a striking effect on skin lesions and deserves further study.

RATIONALE FOR FURTHER CLINICAL TRIALS WITH 6-DIAZO-5-OXO-L-NORLEUCINE (DON) – R. Catane, A.A. Ovejera, D.P. Houchens, D.D. Von Hoff, H.L. Davis Jr., M.K. Wolpert, M. Rozencweig and F.M. Muggia, NCI and Battelle, Columbus

Promising antitumor activity has been reported in human colorectal cancer with the glutamine analog azotomycin (A) (NSC-56654) used alone (CCR 52, 611, 1968) or in combination with 5-fluorouracil (CCR 54, 109, 1970) but trials with A were subsequently discontinued because of inadequate drug supplies. In vivo, A may be converted to DON (NSC-7365) which could be the active component of A. The present experiments were carried out to compare the antitumor effect of A and DON a gainst four human tumor xenografts in nude mice, i.e., CX-1, CX-2 (colon adenocarcinomas), MX-1 (breast infiltrating duct cell carcinoma) and LX-1 (lung small cell carcinoma). All these xenografts exhibit high rates of positive take (more than 95%) and short volume doubling time (4.5-5.5 days). Nude mice of random bred NIH Swiss background were implanted subcutaneously with tumor fragments. Treatments with A and DON, both given at 25-100 mg/kg/injection q 4 days x 3, were initiated when the xenografts became palpable and were growing progressively. CX-1 showed sensitivity only to DON given at the highest dosage level. In CX-2, a definite tumor regression was achieved with DON while only tumor growth inhibition was seen with A. In MX-1 and LX-1, both A and DON elicited marked tumor regression at all dosage levels. Neither drug induced toxic effects in most of the animals with the dose schedules investigated. These experiments suggest a superior anticancer potential of DON as compared to A. The overall data stress the need for additional clinical trials with several schedules of DON, a drug that has not yet been adequately investigated in a number of human tumor types including colorectal, breast and small cell lung cancer.

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