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"CRITICAL ISSUES" INCLUDE HOW U.S. NCI SPENDS ITS MONEY, "CATASTROPHIC" CUTBACK IN CANADA

The key session on "Critical Issues in the Development of National Cancer Research Programs" at the annual meeting in Toronto last week of the American Assn. for Cancer Research focused on one major theme –financial support, lack of it, and how the dollars are distributed.

"The recent freeze on Canadian federal government research funds is catastrophic," said Douglas Waugh, president of the National Cancer In-

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In Brief

O'CONOR NOW TOP PROSPECT IF RAUSCHER LEAVES; FLOOD GIVES NCI INCREASE OF ONLY $11 MILLION

GREGORY O'CONOR, NCI associate director for international affairs, now looms as a top prospect for director if Frank Rauscher leaves. O'Conor had tentatively accepted an offer to head the comprehensive cancer center at Denver, but negotiations fell through and he decided to remain at NCI. O'Conor is an MD, on good terms with NCI senior executives, and well acquainted with foreign cancer scientists and health officials. . . . **RECRUITMENT** of a deputy director for Div. of Cancer Treatment Director Vincent DeVita, to replace Stephen Carter, who leaves July 1, is hung up until Rauscher's fate is determined. No one will take the job while the possibility still exists that DeVita might move into Rauscher's position, with the prospect that a new DCT chief would want someone else for deputy. The same factor could hamper the hiring of a clinical director, although a search committee has a prime candidate and DeVita is in the process of selling him on it. . . . **NCI RECEIVED** only an $11 million increase for fiscal 1977 over 1976 in the appropriation bill marked up by Chairman Daniel Flood's House HEW Appropriations Subcommittee last week. The increase for all of NIH is $99 million. NCI's total, $773 million, "will leave us much more strapped than we've ever been, unless the Senate puts a lot more in," Rauscher said at the AACR meeting. "We need $100 million more just to keep up with inflation." NCI had asked for $948 million, and the President had chopped that request to $687 million. . . . **FINAL CIDAC** contract awards are now in negotiation between NCI, M.D. Anderson and Franklin/Wistar. The MDA contract for establishing and operating a Cancer Information Dissemination and Analysis Center–primarily, searching the literature and compiling abstracts–will cover cancer therapy, rehabilitation and prevention. Franklin/Wistar, in Philadelphia, will cover the fields of virology, immunology and biology. NCI had previously awarded a contract to Stanford Research Institute to cover carcinogenesis. The CIDACs will be compiling an estimated 2,000 abstracts a month, screening them for relevancy to particular areas of interest, and sending them to investigators in their respective fields. The system should be fully operational by the end of the year.

RAUSCHER SAYS SOME CONSTRUCTION FUNDS MAY GO TO TRAINING, CENTERS

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stitute of Canada. "It is the start of a long illness from which recovery will be long and difficult. Dismantlement of the research community is something we can ill afford, and is the single most difficult issue we face."

Waugh mentioned as other issues the need to provide cancer researchers, "whose productive years in the field range from 10 to 30 years," with careers which they can "pursue with dignity" when their productive years in oncology end; and peer review, "in which the decisions of the reviewers become the policies of the agencies and in which the biases and foibles of the reviewers become the biases and foibles of the agencies."

NCI Director Frank Rauscher noted that the major philosophy of the National Cancer Program is to "do everything possible with existing technology for the benefit of the cancer patient while putting as much of our resources as possible into basic research. That involves the difficult issue of balance."

Rauscher said he hoped to provide more discretionary funds to center directors, more money to cooperative groups and more money for training programs. "If necessary, we'll take funds out of construction and put it into training," he said. "People are more important to the success of the cancer program than bricks and mortar."

In defense of NCI's construction aid program, Rauscher said that the $155 million that has gone into it since 1972 has been well spent and has helped attract at least another $200 million from state and local sources.

One of the most important special authorities granted NCI by the National Cancer Act is the submission of the budget request directly to the President, Rauscher said. The report of the President's Panel on Biomedical Research, which has been submitted, recommends that NCI retain that authority and all other mandates in the Act, Rauscher said.

"It's a myth that Congress is against basic research," Rauscher said. One reason why the Cancer Control Program is so important is that "as long as we can convince Congress and the public that we are tranferring technology widely and rapidly, we'll get all the money we need for basic research."

Thomas King, director of NCI's Div. of Cancer Research Resources & Centers, said of the traditional, investigator-initiated research program, "We consider this the primary instrument for advancing biomedical knowledge."

King explained NCI's decision this year to fund traditional research grants at 80% of the recommended funding level, a decision that had grantees at the meeting doing considerable grumbling. "It was the only way to fund a respectable number of new grants," King said. In the current fiscal year, NCI is funding 44% of approved new traditional research grants and 60% of competing grants. Rauscher agreed with critics in the audience that "anytime in an extramural program you can only pay 38-40% of approved applications, you are not going very far down the priority list. You know there are a lot of good ideas and good people not being funded."

Reprogramming funds is one way, Rauscher said, but it takes 18-24 months to phase out contracts. There is not a lot of reprogramming leeway, with all the commitments and congressional mandates.

"Where would I get the money? Take it out of the Carcinogenesis Program? If I did that, Congress would have my head," Rauscher said.

Participants in the meeting directed most of their questions, and criticisms, at Rauscher and King. One said he takes exception to the philosophy of doing something for cancer patients now at the expense of basic research, "since we are not doing a hell of a lot for cancer patients now." He criticized the judgment involved in distributing the $74 million NCI received over the Administration request, outlined earlier by Rauscher, as not providing enough for grants.

Rauscher responded by noting that the NCI budget for basic research this year is $400 million, compared with the total NCI budget of $181 million in 1971. The largest single amount of the $74 million—$22.3 million—went into regular grants. "And I disagree that nothing is being done for patients. A lot is being done." He cited breast cancer treatment and other areas of progress in treatment.

The question was raised on what NCI is doing about overcoming the legal restrictions against providing certain chemicals to grantees and other investigators in carcinogenesis. NCI now may provide them only to contractors and other government agencies (***The Cancer Letter***, May 7). Umberto Saffiotti, Carcinogenesis Program director, said that staff members are working with Congress on that problem. One approach is to request House and Senate Appropriations Committees to include in their reports on the upcoming money bills a statement clarifying the intent of Congress.

Henry Kaplan, Stanford, noted that he had participated in the original effort to develop the National Cancer Plan and in the subsequent updating of it. He said that all suggestions incorporated into the plan were for projects perceived by those working on it as of the highest priority. "That deprives the instrument of priority judgments," Kaplan said. "Priority decisions are thus made by NCI based on management considerations. Because of this, the plan is an unwieldy document for scientists. How long before scientists come to regard it as a meaningless document, and this then gets out to the public and Congress?"

Rauscher described the plan as a "good assessment of the state of the art. It can't be used to direct re-

search in the future." He said that with peer review of grants and 62 contract review committees comprised mostly of non-NCI personnel, "I can't imagine those people checking the plan first" before awarding grants and contracts. "I think it is important to continue to reassess the state of the art" by periodically updating the plan.

John Higginson, director for the International Agency for Research on Cancer, said he was "disturbed at the trend of the conversation. There's too much defensive thinking. A lot has been done in the last 35 years. We're up against the wall because people have been led to expect miracle cures. That could result in a loss of confidence. It is the duty of this society to ensure that its members' research has some long term application. When an investigator accepts funds for research, he automatically must apply that research to a goal."

Arthur Holleb, senior vice president of the American Cancer Society, presented the ACS list of critical issues. The ACS approach to cancer includes research, education and service, with research as the most costly. "Critical issue—we wish there were more money," Holleb said. ACS constitution and bylaws require that at least 25% of all collected funds be assigned to the research program. The figure actually is 30-31%, Holleb said. Primary responsibility for managing research activity is vested in a national program rather than in the 58 divisions. "Critical issue—it should not be a local program," he said.

ACS support for research and clinical investigation grants totaled $18.7 million last year. Other less well known grants "are critical issues because other sources do not provide adequate support," Holleb said. These include postdoctoral fellowships, faculty research awards, scholars in cancer research, research professorships, institutional research grants, and special grants to support miscellaneous activities.

FREIREICH'S SEVEN LAWS CHALLENGE THREATS TO CLINICAL INVESTIGATION

Seven obstacles that "threaten to choke off the significant clinical research which is essential to our ultimate goal of the control of cancer" were described by Emil Freireich in the David A. Karnofsky Memorial Lectureship at the annual meeting of the American Society of Clinical Oncology.

"I think the time has come to change directions—to swing the boat 90 degrees back toward the type of clinical research that is more observational, and I propose that such a change will keep us relentless on target to our goal of cancer control," Freireich said.

Freireich, chief of developmental therapeutics at M.D. Anderson, is noted for willingness to challenge accepted practices and to question popular theory. The seven obstacles cited in his talk, "Who Took the 'Clinical' out of 'Clinical Research'? Mouse vs. Man" and which led to the development of "Freireich's Seven Laws" were:

- "Opressive regulation" of the clinical investigator, primarily by the federal government, with the most serious problem being FDA's regulation of drug development. "Another area of regulation that has become sufficiently oppressive so that the conduct of clinical research is threatened is informed consent." Acknowledging the "wisdom and importance" of informed consent, Freireich said that "agressive implementation of such regulations has resulted in an extraordinary mountain of bureaucratic excess, which has itself become a significant impediment to research." Law No. 7 is a refutation of "the Regulator's Creed—the general solution to a specific problem will soon become a specific problem requiring a general solution." Drug review and informed consent procedures are designed to protect against the occasional abuse, he suggested. "It is a great human weakness to generalize from exceptions. As scientists, we know that the best solution to a specific problem is a specific solution. We should attempt to prescribe regulatory procedures which accomplish our objectives without interfering with research."
- "A second major obstacle to clinical research is the current clamor for 'primary health care' . . . The clinical scientist is viewed as a super specialist, completely isolated from the problems of illness and health care." Freireich's Law No. 6: "The best patient care, or patient service, is clinical research. If there is documented progress from the discovery of new treatment, then it should follow that the patients participating in such research are themselves the beneficiary of those new advances, in contrast to those patients not participating in clinical research."
- Freireich said he was concerned about generalizations being applied to priorities in cancer research. In choosing priorities, he offers as a guide Law No. 5 —instead of the admonition that the physician should as a first principle "do no harm, a particularly offensive admonition since that requires no action at all," he suggests, "Do what can possibly be done, more important, do that which is necessary. We cannot turn our backs on any part of the cancer problem. We must investigate problems in the clinic as they present themselves. We are required to care for the elderly and the young, for acute leukemia and for lung cancer. . . . The clinical scientist must be in the vanguard of physicians, emphasizing the prospects for a continuously improving outlook and for the achievements of clinical research."
- Freireich attacked the use of concurrent controls and randomization. "When the physician's judgment is that the benefit-risk favors the developmental therapy, then to ask the patient to consent to receiving therapy which in that physician's judgment is inferior, would not be honest . . . blind studies should be done rarely if ever." Physicians who recommend new or developmental therapy should be convinced that the probability is greater for benefit than risk. "In the

absence of that conviction, I don't honestly believe that the physician should offer the patient the extra risk of developmental therapy." He defended the use of historical controls. Freireich's Law No. 4: The best therapeutic research gives the best results.

• Freireich described a "good is bad, bad is good" principle which invalidates results because concurrent randomized studies are not conducted. Referring to two clinical research projects—granulocyte replacement and reverse isolation procedures to diminish infectious complications, "we found that by objective criteria such as survival, frequency of complete remission, frequency of infections, the eventual outcome was substantially better than the historical control data." Yet the academic judgment was that the research was bad, although it gave good results. Other classical clinical trials were conducted over the next 10 years, randomly allocating half their patients to the conventional treatment and the other half to the new. "In both instances, these studies unambiguously confirmed the positive results already published. They did, however, have a bad result—half of their patients had unfavorable results." Law No. 3: "If we must experiment with patients to obtain medical information, then we had best do without that information. It cannot be necessary to have a bad result before we can be convinced of the good results."

• Freireich referred to the problems of false-positive, false-negative findings. The classical approach uses the null hypothesis, in which the investigator hypothesizes that no difference exists and the test is made to reject that hypothesis. "This type of thinking emphasizes lack of willingness to make a falsely positive error." But Freireich insisted that when there is a false-positive error, it is quickly found in subsequent studies, since others will be anxious to try the new therapy. However, a false-negative finding will rarely be disputed, since it is not likely confirming studies will be undertaken. "The investigator's greatest fear should be a false-negative result, and his efforts should be aimed at protecting against that risk." Law No. 2: "Always be prepared for success, because failure creates few problems. . . If the clinical investigator is not optimistic in his choice of new treatments for his patients, who in the health care system will be? We have to offer this optimism to our patients so that they also feel that the drugs to which they are being exposed and the treatments which they are receiving do have prospects for dramatic changes in outcome for the better. There have been dramatic breakthroughs in the clinical investigations of cancer and virtually all of these have been initiated by optimistic individuals in sequential series of patients, making quantitative observations. A strategy which has been effective in the past and will be effective in the future."

• Ethical aspects of clinical research—"commitments to our patients, our institutions, our community and even to the world of man"—led to Law No. 1—"The Clinical Investigator's Creed: The primary beneficiary of clinical research is the patient participating in that research." Justifying certain types of experimental plans because of commitments to future cancer patients or to science "is the first step on a slippery slope toward experimenting on people which ends in violating all of the other six Freireich Laws. The first consideration of a clinical investigator must always be the welfare of that person. Other considerations, while important, must always be secondary."

TREATMENT PROGRESS DRAWS RECORD TURNOUT FOR ASCO; REPORTS PRESENTED

Recent progress in the treatment of cancer and prospects for further progress apparently were responsible for drawing a record turnout at the annual meeting of the American Society of Clinical Oncology, held in Toronto last week in conjunction with the annual meeting of the American Assn. for Cancer Research. More than 2,000 signed up for the ASCO sessions, 800 more than the membership of the organization.

Reports on selected presentations dealing with treatment advances follow here. Other reports and abstracts of many of the papers presented at both the AACR and ASCO meetings will appear next week and in subsequent issues of ***The Cancer Letter.***

• **Platinum Treatment of Testicular Cancer**

Investigators at Memorial Sloan-Kettering and Roswell Park reported on separate studies involving the use of platinum in testicular cancer therapy.

Claude Merrin, chief of urologic oncology at Roswell Park, has developed a new administration technique avoiding the kidney and hearing toxic damage of cis diamine platinum. "At present there are no apparent limitations to the total dose of platinum that can be administered," he said.

Merrin based his study upon nine patients who have received platinum. All nine patients had recurrent and widespread testicular tumors and had been treated already with other chemotherapeutic agents, surgery and/or radiation. After evaluating kidney and hearing function, these patients were given platinum and effective diuretics enhancing kidney function in a solution over a period of hours. Five patients were treated twice a week for three weeks and then once a week thereafter. The other four were treated once a week.

Complete remission was achieved in five patients and objective response (50% decrease in disease) was observed in three patients. In one patient, no response was seen. Moderate side effects as expected by this drug (drop in white blood count) were seen after several doses, however, no kidney or hearing toxicity was seen.

About 93% of the patients on a new combination drug therapy, including cis-platinum, for cancer of the testes have shown positive responses, Esteban

Cvitkovic of Memorial Sloan-Kettering reported.

The new therapy, called VAB III, is the third refinement of a protocol that began in 1971. One of the major changes in the therapy is the addition of two more drugs, cis-platinum and cyclophosphamide, and the reintroduction of a third, chlorambucil.

Cvitkovic said that treatment of 40 patients with advanced metastatic germ cell cancers has shown that the new drug therapy produced complete remissions in 23 men. Twelve more patients showed partial remissions and are still improving, and two others improved somewhat. Patients have been followed for up to 10 months.

VAB III is the third generation of a therapy that began with vinblastine, actinomycin D and bleomycin. It has been highly effective even in patients who were previously treated. Fully 90% of these men responded to the drugs. This is highly significant because previously treated patients often build up resistance to drug therapies. To prevent resistance, Memorial physicians frequently rotated the active drugs, Cvitkovic said.

VAB III begins with eight days of concentrated drug therapy during which the tumor starts to shrink in size. The patient is then off drugs for two or three weeks to lessen the chance of severe toxic reactions and to prevent the development of drug tolerance. In the maintenance phase, five drugs in a specific sequence are used to consolidate the gains made in the first part of the therapy. The initial sequence is then repeated. Finally, the patient is put on a three-drug course that lasts about two years more. The men are on drug therapy for three years. They receive most of their treatment as outpatients. To prevent the toxic effects of platinum, mannitol, a diuretic, was administered.

• **MOPP Vs. Hodgkin's Disease**

Advanced Hodgkin's disease is curable with a four-drug combination (MOPP) in more than half of all treated patients, Vincent DeVita, director of NCI's Div. of Cancer Treatment, reported. His remarks were based on 10-year survival data from a study conducted in DCT's Medicine Branch.

While early stages of Hodgkin's, those limited to a confined area of the body, can be treated effectively with radiation therapy, fewer than 10% of patients with advanced disease have survived five years when treated with either radiation therapy or single anticancer drugs. Virtually no patient with widespread disease—stages III and IV— survived free of disease beyond five years.

A treatment program for advanced Hodgkin's disease, consisting of four drugs (nitrogen mustard, vincristine (oncovin), procarbazine and prednisone, called MOPP) was begun at NCI in 1964. None of the 194 patients included in the analysis had significant therapy prior to receiving MOPP.

Eighty-one percent (155 of 194) of patients treated with MOPP achieved a complete remission. This is a fourfold increase over remissions achieved with single drugs, DeVita said. Of the 155 patients who achieved a complete remission, 82% are alive at five years after all treatment was stopped, and 72% of those patients at risk are alive at 10 years. Sixty-six percent of these patients are in their first complete remission at five and 10 years. In sharp contrast, no patient who failed to achieve a remission with MOPP is alive at five years.

DeVita and his colleagues analyzed the data for factors that might influence the completeness of a patient's response to the multiple-drug chemotherapy. These factors include age, sex, stage of disease when treated, microscopic appearance of the lymph node, involvement of organs other than those in the lymphatic system and presence or absence of symptoms.

Symptoms of Hodgkin's disease that usually appear in later stages of the disease include fever, weight loss and night sweats.

The presence of these symptoms was the only factor that influenced the ability of a patient to achieve a complete remission, DeVita said. Fully 100% of the 22 asymptomatic patients achieved a complete remission, while 77% of patients with symptoms achieved a complete remission.

Duration of the first complete remission was also influenced by the presence of symptoms. All 22 asymptomatic patients remain in their first remission at five years, while 60% of patients with symptoms are in complete remission at five years. Histology also played a role in the continuous disease-free status, DeVita noted. Patients with nodular sclerosing Hodgkin's disease had shorter complete remissions than patients with either of the other three histologic variants: mixed cellularity, lymphocyte depleted or lymphocyte predominant.

Because nodular sclerosing is a more indolent form of the disease, overall survival was not affected by histology at either five or 10 years. Poorer survival did correlate with the presence of symptoms, however.

Median survival, the length of time that half of the population of patients lives, has not been reached in the study. Sixty-five percent of all 194 patients are alive at five years and 58% at 10 years. No one who has remained in complete remission for 3½ years following treatment has relapsed.

• **Coformycin Vs. ALL**

A possible "biochemical handle on lymphocyte metabolism" with therapeutic implications for acute lymphocytic leukemia was discussed by John Smyth of NCI. A new antibiotic, coformycin, inhibits adenosine deaminase (ADA) activity, thereby preventing the conversion of adenosine—which is lymphocytotoxic—to inosine, consequently interfering with reproduction of the lymphocytic series without effect on other blood cell types.

Smyth, a visiting fellow at NCI, found during previous investigations while at the Royal Marsden

Hospital in London that adenosine deaminase activity was increased by 23-fold in 16 acute lymphocytic leukemia patients over the mean ADA activity in 13 healthy controls.

This is in contrast to the situation observed in some cases of combined immunodeficiency disease (CID), in which there are no lymphocytes and a genetic absence of ADA. Other studies showed that the complete absence of lymphocytes was not the cause, but possibly an effect of the low ADA titer in CID patients.

Reasoning along these lines, interference with ADA activity could cause selective lymphocytotoxicity.

Tissue culture studies involving murine leukemic L1210 and L5178Y lines and mitogen-stimulated human lymphocytes in tissue culture showed that these cells also had high ADA activity.

In vitro exposure of the two murine cell lines to adenosine demonstrated that concentrations of adenosine above 10^{-5}M inhibited cell division, with the toxic effect inversely proportional to the intracellular ADA activity, Smyth said.

Interference with ADA activity to break down adensine using coformycin in the tissue culture systems resulted in arrest of reproduction of the lymphocytes. Inhibition by doses of coformycin as low as 10^{-8}M produced a five-fold increase in the toxicity of 10^{-4}M adensine to the lymphocytes and potentiated adensine-induced inhibition of ^{3}H-thymidine incorporation into mitogen-stimulated lymphocytes.

Coformycin inhibited DNA synthesis in phytohemagglutinin-stimulated lymphocytes by a factor of 95 to 99% when given in doses as low as 10^{-6} to 10^{-8} M, without the addition of any extraneous adenosine.

NCI investigators are currently working to synthesize coformycin so that it can be used in expanded animal trials and toxicity studies. The structure of the drug, developed in Japan, is known but it is not readily produced.

Thus far, the substance is the "most powerful inhibitor of adenosine deaminase yet discovered," according to Smyth.

Potential for use is as an immunosuppressant acting directly on lymphocyte production following organ transplants as well as a specific lymphocytotoxic agent against lymphocytic leukemias.

• **New Protocol for Non-Hodgkin's Lymphoma**

Results from a promising new drug protocol for treating non-Hodgkin's lymphoma was reported by Norma Wollner, Memorial Sloan-Kettering pediatrician. Wollner said that about two-thirds of her patients with advanced non-Hodgkin's lymphoma are now free of cancer for an average of 26 months following administration of a new multiple drug therapy she devised.

The new drug protocol consists of high doses of cyclophosphamide that reduces the bulk of the tumor, followed by a program of 10 other drugs. About three weeks into the therapy, surgery is performed to remove whatever bulky cancer remains, or radiation is directed to the site of the original tumor. The drugs are given throughout the period of surgery and radiation. Patients continue on the drugs for two or three years.

"This is an aggressive therapy, but we found that the youngsters tolerated it well and improved rapidly," Wollner said. "Earlier therapies, which were often modeled on treatments for Hodgkin's disease, simply were not strong enough to fight non-Hodgkin's. We needed a therapy as aggressive as the disease."

Sixteen children with disease too advanced for surgery were included in the study, which began in 1971. Twelve of that group (75%) are now completely free of the disease, for periods that range from six months to almost five years.

The length of the remissions is particularly encouraging, Wollner said, because if non-Hodgkin's does recur after treatment, it generally does so soon after the initial remission. She noted that, in comparison to these results, an earlier study she conducted with a different therapy for abdominal non-Hodgkin's lymphoma showed only one patient (7%) had a remission.

Wollner and her colleagues developed the basic outlines of the new protocol in 1971. Earlier, they had used several other therapies including one with cyclophosphamide and radiation therapy. This produced an average survival of about 11 months.

To improve these results, they added the drugs used for leukemia to the cyclophosphamide and radiation protocol. "We included the leukemia protocol because non-Hodgkin's lymphoma spreads to bone marrow where blood cells are produced."

As in the leukemia protocol, intraspinal methotrexate was added to the therapy to prevent spread of the cancer to the brain, a generally fatal development. With these changes, results improved dramatically. Recently, the use of surgery and radiation was modified to remove traces of the primary tumor left behind after initial drug treatment.

• **Reducing Kidney Damage from Methotrexate**

Susan Pitman, D. Landwehr, N. Jaffe, and E. Frei, Harvard, reported on a method they developed to reduce the kidney toxicity of methotrexate.

High dose methotrexate with citrovorum factor rescue has been shown to be effective in the treatment of osteogenic sarcoma in children and in squamous cell tumors in the head and neck area in adults. In an earlier study, they had shown that this therapy frequently results in deterioration of kidney function. Renal damage was present in 75% of patients, thus preventing the body of ridding itself of the drug, since in man, the drug is almost 100% excreted by the kidney. Since methotrexate does not stay in solution at an acid pH, they postulated that in acid urine, the drug might be precipitating out of solution as the kidney was ridding itself of the drug, and that

the precipitated drug was causing partial blockage of the kidney, thus causing renal damage.

Hence, using sodium bicarbonate orally, the urine was alkalinized and patients instructed to keep their urine pH greater than or euqal to 7 and instructed to push p.o. fluids at home.

The results indicate that when one compares the 59 alkalinized adult patients who received 364 courses of weekly methotrexate to the 33 nonalkalinized who received 73 courses, it is evident that alkalinization of the urine has decreased the frequency of kidney damage, thereby allowing individual patients to receive many more courses of the drug and indirectly allowing the patient's tumor to have a greater chance to respond to the drug. In fact, nearly half of the patients, 24 of 49, have had responses, which while of short duration, are encouraging—including patients with non-Hodgkin's lymphoma, breast cancer and squamous cell carcinoma of the head and neck as well as sarcoma, eat cell carcinoma, gastric adenocarcinoma, choriocarcinoma and ovary.

By close monitoring of kidney function tests (serum creatinine) one day after methotrexate, they have been able to predict patients at risk for toxicity and have also been able to prevent toxicity by prompt increase in the frequency, amount, and duraction of the leucovorin (rescue) administration, in a group of patients who otherwise become uniformly toxic with drop in peripheral blood counts and oral ulcers.

• **Drug Therapy Vs. Neuroblastoma**

Lawrence Helson, Memorial Sloan-Kettering pediatrician, reported that more than 90% of his neuroblastoma patients with especially poor prognoses improved significantly with a new combination drug therapy.

Neuroblastoma affects children generally before the age of five. It is almost always fatal when diagnosed in youngsters over two, the group Helson is working with. "Surgery, radiation and a variety of drugs have not appreciably altered the virtually zero cure rate for these children," he said.

Twenty-eight patients over two, with cancers that had already spread, were included in a study, which began in August 1974. Therapy consists of very high doses of several drugs for four days, followed by a three to four week rest. The cycle of drugs and rest is repeated monthly. Twenty-six of 28 children responded to the therapy, with almost complete elimination of clinically detectable tumor.

Ten of 12 previously untreated and nine of 16 previously treated patients are free of disease, for up to 18 months. Patients who had previous drug treatment often develop some resistance to therapy.

In neuroblastoma, nerve cells continue to replicate after birth. In normal infants the process ceases by the time the child is born. The N3 protocol, as this neuroblastoma therapy is called, stops the replication and causes the cells to act benignly. This taming of the outlaw cells is accomplished by administering the largest drug doses the patient can tolerate.

Such doses, however, are highly toxic, often killing the white blood cells that make up the body's immune system. The patient is then more vulnerable to infections. More importantly, it is possible for transfused blood or platelets to trigger a "graft vs. host" reaction.

To prevent this, Helson irradiates all blood and platelets before they are given to the patients. Irradiating the blood kills the potentially lethal white blood cells. He also carefully monitors the doses of toxic agents and administers antibacterial and antifungal drugs to prevent infections.

The N3 protocol is the third refinement of a program that began at Memorial Sloan-Kettering in 1967. The therapy consists of cyclophosphamide, vincristine, trifluorothymidine and papaverine.

• **Measuring Tumor Cell Growth**

The radioisotope tritiated thymidine is the most widely used isotope in man. The isotope is incorporated into DNA, the genetic material in the cells responsible for cell reproduction. By injecting patients with tritiated thymidine it is possible to accurately measure the growth rates of tumor cells as compared to various normal cells. It may be useful for determining the effect various treatment regimens have on tumor growth. Stephen Straus, Barnes Hospital, St. Louis, and Marc Straus, Boston Univ. Medical Center, injected nine patients with malignant disease with tritiated thymidine. They determined that only 12% of the injected dose was taken up into DNA, and most of the isotope was excreted in the urine. The radiation dose to the cells was only a few times higher than a patient ordinarily receives from diagnostic tests such as a mammogram or barium enema.

CONTRACT AWARDS

Title: Mechanisms of lymphoid cell differentiation
Contractor: New York Univ., $150,691.

Title: Immunotherapy: Role of circulating tumor antigens
Contractor: Univ. of Minnesota, $90,779.

Title: Isolation of antineoplastic agents from plants
Contractor: Purdue Research Foundation, $386,889.

Title: Chemotherapy of ovarian carcinoma
Contractor: Mount Sinai School of Medicine, $37,520.

Title: Studies and investigations on endocrine therapy plus chemotherapy in patients with breast cancer
Contractor: Univ. of Minnesota, $87,500.

Title: Study of role of stroma in the growth of neoplastic and preneoplastic lesions of the mammary gland
Contractor: Stanford Univ., $89,000.

Title: Investigation of a slit-scan technique as a basis for an automated prescreening system for cancer detection in cytology
Contractor: Univ. of Rochester, $275,132.

Title: Establish and maintain a cancer radiation therapy center
Contractor: Mary Hitchcock Memorial Hospital, Hanover, N.H., $496,000.

Title: Human tumor associated antigens and corresponding antibodies
Contractor: Karolinska Institutet, Stockholm, $55,000.

Title: Group testing for screening of carcinogens
Contractor: UCLA, $94,704.

Title: Immunologic study of RNA (type C) viruses
Contractor: Scripps Clinic & Research Foundation, $356,888.
Title: Hapten treatment of cancer
Contractor: Univ. of Pennsylvania, $72,225.

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 NCI-CP-VO-71000-67

Title: *Support effort for coordinated processing of human specimens*
Deadline: *June 18*

NCI is interested in contracting with a local organization within 25 miles of NIH to obtain assistance in the pickup, handling, processing, and distribution of human neoplastic and normal specimens for use in cancer research. Respondents should have a background experience in tissue culture and knowledge of medical terminology to provide the coordinated distribution of appropriate specimens as directed by NCI.

The successful organization will be required to handle approximately 250 specimens per month. Respondents should possess the ability to perform specimen evaluation, have the technical competence to handle sterile tissue culture material, and be able to maintain records of receipt, distribution, and processing.

Contract Specialist: D.M. Coleman
Cause & Prevention
301-496-1781

RFP DAMD17-Q-6562

Title: *Evaluation of differences in mammalian metabolism of trinitrotoluene (TNT) as a function of route of administration and carcinogenesis testing*
Deadline: *June 4*

The study consists of two phases. The first is designed to determine whether exposure to TNT in inhalation chambers produce identical metabolic products in similar proportions to that produced with animals given TNT orally. The ultimate goal is to determine whether a feeding study serves as an adequate model for occupational exposure to TNT to test for the induction of leukemia. In Phase II, using the model developed in Phase I, a carcinogenesis test is to be conducted using TNT.

Contact: Contracting Branch
Logistics Division
U.S. Army Medical Research & Development Command
Washington, D.C. 20314

SOLE SOURCE NEGOTIATIONS

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

Title: Characterization of polymerase product and other inhibitors
Contractor: Litton Bionetics.

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

Title: Programming services in support of contract management system
Contractor: Sigma Data Computing Corp.

Title: Development of propagation procedures, purification and characterization of viruses
Contractor: Electronucleonics Laboratories.

Title: Cancer control assistance program for community health professionals
Contractor: Assn. of Community Cancer Centers.

Title: Inelastic laser light scattering studies on nucleic acids, nucleoproteins, and viruses
Contractor: Michigan Cancer Foundation.

The Cancer Letter—*Editor* JERRY D. BOYD

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