THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 3 No. 18

May 6, 1977

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

Subscription $100 per year

DIET & NUTRITION, CARCINOGENESIS, VIRUS, TOBACCO COMMITTEES PROPOSED FOR ELIMINATION

Four major NCI advisory committees were proposed for elimination by Acting Director Guy Newell following orders by the Carter Administration to reduce the size and number of such groups (*The Cancer*

(Continued to page 2)

In Brief

HARVARD'S RICHMOND SAID TO BE THE CHOICE AS ASST. SECRETARY; LEE CLARK CONVALESCING

DOES CALIFANO finally have his asst. secretary for health? The longest running suspense saga of the Carter Administration in which several health leaders turned the job down and one accepted and started to work but quit before the Senate confirmed him, now involves Julius Richmond of Harvard. The *Washington Post* reported that Richmond, head of Harvard's Dept. of Preventive & Social Medicine, has agreed to take the job. So far, no one at HEW has denied it. Richmond, 60, was first director of the Head Start Program in the Kennedy Administration. . . . **"HOW TO"** of Hospice Care is the theme of a conference May 26-28 in San Rafael, Calif., sponsored by Hospice, Inc. of New Haven, Conn., Palliative Care Service of Royal Victoria Hospital in Montreal, and Hospice of Marin, Calif. Lectures will be given on needs of the terminally ill, what a hospice is and isn't, obstacles to hospice development and value of a team approach. Feasibility of forming a national organization for hospices will be discussed. Contact David English, Hospice of Marin, P.O. Box 72, Kentfield, Calif. 94904. . . . **MAXINE SINGER**, head of NCI's Nucleic Acid Enzymology Section, will deliver the G. Burroughs Mider Lecture May 18, 8:15 p.m., at NIH. Her topic is "Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA" . . . . **ROBERT MILLER** of NCI's Clinical Epidemiology Branch, wrote in a guest editorial in the March issue of *Journal of NCI:* "There is a close correlation between the Ames test of mutagenicity and carcinogenicity in experimental animals. The overlap is substantially less when all known human carcinogens are considered, in large measure because the test procedure is not appropriate for these agents. Germinal mutations account for a relation between certain malformations and cancer. These relationships have provided new insights into the carcinogenic process. By contrast, little new insight has yet come from studies of the capacity of a few environmental agents to induce both cancer and congenital malformations. The situation should change with advances in research by clinicians, epidemiologists and laboratory scientists, if only they would talk to one another" . . . . **R. LEE CLARK**, president of the Univ. of Texas System Cancer Center, is recovering from arterial bypass surgery at St. Luke's Hospital in Houston. The hospital says he is "doing well" but will not get back to work for several weeks.

GORI LOSES HIS THREE COMMITTEES, BUT SAYS HE'LL GET BY WITH AD HOC GROUPS

(Continued from page 1)

Letter, April 22).

The four to be eliminated are the Carcinogenesis Scientific Advisory Committee; the Diet, Nutrition & Cancer Program Advisory Committee; the Tobacco Working Group; and the Virus Cancer Program Advisory Committee.

All four deal with programs housed in the Div. of Cancer Cause & Prevention. Three of the programs are directed by DCCP Deputy Director Gio Gori; the fourth, the Virus Cancer Program, is headed by John Moloney, associate director for viral oncology.

Twenty-one other NCI committees are involved in mergers in Newell's plan. They are;

- The Breast Cancer Diagnosis, Epidemiology, Experimental Biology and Treatment committees will be consolidated into one.
- The Cancer & Nutrition and the Diet & Cancer Scientific Review Committees will be merged.
- The Carcinogenesis Program Scientific Review Committees A and B will be merged.
- The Developmental Therapeutics and Drug Development committees will be merged.
- The Diagnostic Radiology Committee and the Diagnostic Research Advisory Group will be merged.
- The four organ site working cadre groups—Bladder, Prostatic, Large Bowel and Pancreatic—will be consolidated.
- The Virus Cancer Program Scientific Review Committees A and B will be merged.

The Temporary Review Committee for Frederick Cancer Research Center and the Temporary Cancer Institutional Fellowship Review Committee both will be eliminated. As their names indicate, they were not going to be around very long anyway, so including them in the list was window dressing.

HEW reportedly has approved the NCI proposal along with other cuts at NIH, FDA and elsewhere in the department. The proposals are now waiting action by the Office of Management & Budget.

Newell is certain to be criticized by committee members and other constituents of the programs, and possibly by Congress, for dropping the Carcinogenesis, Virus, Tobacco and Diet & Nutrition groups, particularly the last. The D & N Committee, bitter about what its members felt was inadequate funding for the program, tried to go over Newell's head on distribution of money in the FY 1977 budget. This brought a sharp rebuke from Benno Schmidt, chairman of the President's Cancer Panel, and admonitions from Newell to that and other committees that "you are advisors, not lobbying groups."

Newell and other NIH executives are under strict orders from HEW not to discuss the proposals until they are approved by OMB. But he told *The Cancer Letter* that "there was no vindictiveness on my part" in determining which committees to eliminate. He said he would explain the rationale for those determinations when OMB takes the lid off.

If anyone had the right to feel paranoid, it would be Gori, with all three of his advisory groups shot down. He has relied heavily on those groups to generate research ideas, to develop project priorities and to critique ongoing research. The Carcinogenesis Committee, chartered only recently, was also expected to provide some review of intramural carcinogenesis research.

Gori said, however, that he did not feel he was being treated unfairly. If the committees are killed, Gori said he would make use of ad hoc committees and workshops to obtain program advice from outside scientists. That, of course, would reduce the amount of money the committee cuts are expected to save—about $800,000 at NCI.

"I'm not paranoid about the Diet & Nutrition committee," Gori said. "I'm sure we weren't singled out. It was just part of a total effort to reduce the number of committees, which I think is a wise policy. But we do have to work through groups of non government scientists. We don't have the expertise for a national effort without it."

Moloney pointed out that his committee, in existence for a little more than a year, was providing a review of intramural virus research in addition to advising on overall program direction.

"The program will continue without it, but it is a good committee and I hate to lose it," Moloney said.

Moloney and Gori also will have to deal with the merging of their technical review committees. They had been split into A and B groups to permit members to enter into competition for contracts without a conflict of interest. If a member of committee A responded to an RFP, his proposal was reviewed by committee B. With one committee, a member submitting a proposal will not be permitted to attend the meeting in which it is reviewed.

Moloney said he felt the new system would work all right provided the committees are large enough. Each committee now has 25 members; he felt that 30 should be enough to include the necessary disciplines and to permit members to stay away when their proposals are reviewed.

The matter of review of NCI intramural research has been a bone of contention with the scientific community for some time. The Virus Cancer Program Advisory Committee was established as one of recommendations of the Zinder Committee, which studied complaints of nongovernment scientists about the program. One of the complaints was that NCI kept too much of the program development to itself; another was that, after the Etiology Program Advisory Committee was dropped, no outside review of Moloney's intramural staff was being done.

Other NCI divisions have Boards of Scientific Counselors specifically charged with periodically re-

viewing intramural programs, as well as providing program direction.

Eight FDA committees were proposed for elimination, most of them due to expire anyway. One that could have some effect on the Cancer Program is the Science Advisory Board to the National Center for Toxicological Research. That board has a subcommittee on bladder cancer. A number of other FDA committees were listed for mergers, but the Oncologic Drugs Advisory Committee was not one of them.

None of the NIH study sections in the Div. of Research Grants was marked for extinction or merger, which leaves the grants review operation intact.

UPTON OF STONY BROOK MAY BE DIRECTOR PROSPECT; CALIFANO HOLDS INTERVIEWS

Arthur Upton, dean of basic science at New York Univ. at Stony Brook, may be the other name on the list of NCI director prospects submitted to HEW Secretary Joseph Califano by his search committee. Arnold Brown is the other.

Upton, 54, is a pathologist and has been involved in various aspects of the cancer program. He recently completed one of three reports dealing with the controversial NCI-ACS breast cancer detection and demonstration program. Upton's report dealt with radiation risk.

Meanwhile, a month after Califano had received the recommendations and had promised to move quickly, he was reportedly interviewing Brown and Upton this week. Neither Brown nor Upton was available to confirm the report by press time (and in any case probably would have been constrained from discussing it, given HEW's penchant for secrecy throughout the search for a director).

Brown had hoped that a decision could be reached by early April, to permit him to accept a two-month visiting professorship at the Univ. of Heidelberg. When that time came and went with no decision, some of his colleagues persuaded him to pass up Heidelberg and wait it out, feeling that his chances of getting the appointment were better than even.

PROGRAMS SET FOR ASCO, AACR, NURSING SOCIETY MEETINGS IN DENVER MAY 14-21

"Some Current Controversies in Oncology" is the title of a three-part symposium at the annual meeting of the American Society of Clinical Oncology in Denver May 16-17. The ASCO meeting precedes the annual meeting of the American Assn. for Cancer Research, also in Denver, May 18-21, and follows the annual meeting of the Oncology Nursing Society, May 14-15. All three meetings will be in the Denver Hilton Hotel.

The controversies symposium includes:

–Perspectives in the primary therapy of breast cancer, chaired by D.C. Tormey, Univ. of Wisconsin Hospital. W.L. Donegan, Medical College of Wisconsin, will speak on surgery; Gianni Bonadonna, Milan, chemotherapy; and A.S. Glicksman, Rhode Island Hospital, radiation therapy.

–Immunotherapy, chaired by William Terry, director of NCI's Immunology Program. Terry will review the present status of clinical immunotherapy; M.J. McKneally, Albany Medical College, regional immunotherapy with bacillus calmette-guerin in lung cancer; J. Cuttner, Mount Sinai, systemic immunotherapy in acute myeloblastic leukemia; and A.L. Goldstein, Univ. of Texas Medical Branch, recent developments in the chemistry, biology and clinical applications of thymosin.

–Controversies in cellular kinetics: reasons for laboratory success but clinical failure, chaired by R.C. Young, NCI. Larry Norton, NCI, will speak on "The Log Kill Hypothesis Revisited: If We Only Saw L1210 Leukemia in Humans;" L.M. Schiffer, Allegheny General Hospital, clinically applicable systems of cell kinetics techniques; and Young, "Human Tumors Rarely Occur in Vitro and Unassociated with Humans."

Frank Rauscher, senior vice president for research of the American Cancer Society and former NCI director, will deliver the annual David. A. Karnofsky Memorial Lecture. His topic: "The National Cancer Program: Reflections and Current Issues."

AACR President Elizabeth Miller will deliver her presidential address on "Current Perspectives on Chemical Carcinogenesis in Man and Experimental Animals."

Paul Carbone, Univ. of Wisconsin, will give the Richard & Hinda Rosenthal Foundation Award Lecture on "Tumor Biology & Clinical Trials."

AACR has scheduled a symposium on the present status and future prospects of immunotherapy, with Robert Good of Memorial Sloan-Kettering as chairman. Participants include James Holland, Mount Sinai, immunotherapy of human leukemia; E.H. Hersh, M.D. Anderson, immunotherapy of human solid tumors; and H.F. Oettgen, detection and definition of human cancer antigens. Good will talk on recent advances in immunobiology and their implications in cancer immunotherapy.

Ludwik Gross, Veterans Administration Hospital Cancer Research Unit in the Bronx, will deliver the G.H.A. Clowes Memorial Lecture on "Viral Etiology of Cancer and Leukemia: A Look into the Past, Present, and Future."

Another AACR symposium is scheduled on cell surface changes and neoplasia, chaired by L. Warren, Wistar Institute. Participants are K.R. Porter, Univ. of Colorado, morphological alterations in the cell surface; C.A. Buck, Wistar Institute, changes in cell surface glycopeptides; I.H. Pastan, NCI, studies on the biochemical basis of the altered appearance of transformed cells; and J.L. Strominger and S.F. Schlossman, Harvard, cell surface antigens of human

lymphocytes.

The Oncology Nursing Society meeting will feature a symposium on models of health care delivery to the cancer patient and family. The program also will include presentation of papers submitted by members on clinical practice and nursing research.

NCI SUPPORTS RETINOID DEVELOPMENT FOR PREVENTION; NO MAGIC BULLET

"Chemoprevention"—the use of drugs to prevent cancer—may be the next new glamour area of cancer research to attract the attention of the public and Congress as well as the scientific community. But if NCI can help it, chemoprevention will not evolve into the magic bullet concept that oversold virology to the public and Congress. Neither will it be given the kind of attention immunology received a few years ago when young scientists were encouraged to jump into that field with assurances that this was the ultimate way to beat cancer.

Michael Sporn, chief of NCI's Lung Cancer Branch who is heading up the new chemoprevention effort, said his program "is more analogous to the fluoridation of water" than to the magic bullet, viral-based vaccine concept. "It will require chronic use and thus demand a great deal of assurances of safety."

Sporn's program in the current fiscal year will spend about $1.8 million in collaborative research, all through contracts. His branch includes four postdoctoral investigators who spend most of their time in the program which basically involves the development and testing of retinoids, synthetic analogs of vitamin A. By NCI standards, it is a modest program, although it could grow quickly in a year or two if progress, and the need for more money, can be demonstrated.

Sporn recently described the rationale for use of retinoids in cancer prevention at the Science Writers Seminar sponsored by the American Cancer Society:

"Retinoids are the family of molecules comprised of both the natural and synthetic forms of vitamin A. Retinoids are known to be required for the normal cell maturation in the epithelial (lining) cells of most of the important organ sites for development of cancer in both men and women. These sites include the lung, colon, breast, pancreas, prostate, stomach, bladder, uterus and esophagus.

"In the absence of retinoids, normal cell differentiation and maturation do not occur. No other class of substances is known to have this essential role played by retinoids in control of differentiation of nearly all epithelial cells. Since the development of cancer involves a de-differentiation (reversal or change of differentiation in epithelial cells), the pharmacological use of retinoids in cancer prevention is an attempt to block or reverse a pathological process by enhancing the normal processes of cell differentiation. These processes are in an abnormal state during the development of cancer because of the exposure of the cells to carcinogen.

"One may visualize two opposing processes occurring in epithelial cells that have been exposed to carcinogens: the normal cellular forces are working to stabilize mature, differentiated states, and the carcinogenic forces are working to changes these states toward malignancy. The retinoids then are working to stabilize the formation of mature, differentiated cells and to counteract the effects of the carcinogens; they thus may be considered to be "anti-carcinogenic" agents. However, their desirable effects are not dependent on their ability to kill tumor cells. It has been shown that retinoids have the direct ability to reverse the premalignant effects of carcinogens in organ culture (in vitro) of both prostatic and tracheal epithelial tissues without killing cells.

"The above considerations have led to the testing of retinoids for prevention of cancer in several epithelial tissues in experimental animals. Natural retinoids, such as vitamin A, which can be bought over-the-counter (retinyl acetate and retinyl palmitate), have been found to have very limited usefulness for cancer prevention. These natural retinoids do not reach the desired target organs in quantities sufficient to be effective, and they are stored in the liver in excessive amounts, where they can cause severe toxicity to the liver.

"Synthetic retinoid analogs, which are chemically related forms, have therefore been made for testing for cancer prevention in animals. Most of these synthetic retinoids have thus far been made by chemists at Hoffmann-La Roche, Inc., Nutley, N.J. and Basel, Switzerland. In contrast to the natural retinoids, the synthetic retinoids can reach desired target organs in higher concentrations and may have less toxic side-effects.

"Up to the present, animal studies have shown that synthetic retinoids may prevent cancer of the lung, bladder, and breast in experimental animals. Different synthetic retinoids have been found to be effective for different organs. When animals have been treated with very high doses of carcinogen, then one finds only a partial protection against development of cancer, such as a lower incidence or a delayed appearance of cancers. When animals have been treated with lower doses of carcinogen, as more closely approximate the human situation, more complete prevention of the development of cancer has been seen.

"In addition to studies on the above organs, experiments are also in progress to determine whether synthetic retinoids can prevent the development of cancer of the colon, pancreas, and esophagus in experimental animals.

"The application of this approach to prevention of cancer in men and women in high risk groups is currently under active consideration. Such groups include industrial workers who have been exposed to

carcinogenic or cocarcinogenic materials, such as asbestos workers or uranium miners, as well as members of the general population who may be at excessively high risk, such as people with premalignant conditions of the bladder or the lung (heavy smokers).

"Since the synthetic retinoids, in order to be effective, will have to be given to people for a very prolonged period (5 years or even more), this preventive approach involves new considerations of benefits vs. risk. In such a situation, there must be the highest degree of assurance that harmful side effects will not result from the daily administration of the drug for prolonged periods of time. The degree of risk of the individual will always need to be assessed against the possibility that the synthetic retinoid might have some undesirable, as yet unknown side effect. A great deal of effort is currently being devoted to develop the safest and most effective new synthetic retinoids.

"One important word of caution: mega-doses of vitamin A, as can be bought over the counter, should not be taken by anyone, since severe damage to the liver may result. Finally, there is no evidence that retinoids of any type are effective for the treatment of invasive, metastatic cancer. Once this type of severe end-stage disease has developed, it must be treated with conventional methods of chemotherapy, surgery, or radiation," Sporn concluded.

NCI has issued three RFPs for Sporn's program:

—Synthesis of new retinoids for in vitro studies of the prevention of lung cancer and other epithelial cancers (RFP NO1-CP-75897-57, ***The Cancer Letter,*** March 25).

—Long term studies of prevention of epithelial cancer by retinoids (RFP NO1-CP-75905-56, ***The Cancer Letter,*** April 8).

—Synthesis of radioactive retinoids for metabolic and pharmacologic studies relating to prevention of lung cancer and other epithelial cancers (RFP NO1-CP-75911-56, ***The Cancer Letter,*** April 22).

Sporn has $700,000 in fiscal 1977 funds available for first year costs of those contracts. That money, incidentally, will come from a pool accumulated by James Peters, director of the Div. of Cancer Cause & Prevention, by skimming across the board from other programs. The pool was established specifically to finance promising new leads, and Sporn competed successfully for it.

Existing contracts include one with IIT Research Institute for long term animal studies, worth about $600,000 a year; and another with Southern Research Institute for organ cell culture, pharmacology and toxicology, worth $420,000 a year. Some work is going on as incidental parts of contracts at Oak Ridge, SUNY (Stony Brook), and Univ. of Vermont. The retinoid portions total about $100,000.

"I'm all for getting rid of carcinogens," Sporn said, "but we will always have some around. There are many situations where they just can't be eliminated. Also, we don't know what is causing many cancers. With bladder cancer, we know that at most, 20% are related to industrial exposure. We don't know what is causing the rest, but we must do something about it."

TREATMENT RESEARCH REPORTS PRESENTED AT SEMINAR; NEW MTX RESCUES NOTED

State of the art reports on research in treatment, diagnosis, carcinogenesis, immunology, genetics, virology, and psychosocial aspects of cancer care were presented by scientists at the Science Writers Seminar.

Summaries of the reports in treatment research are presented here. Other reports will appear in following issues of ***The Cancer Letter.***

CLINICAL AND PHARMACOLOGIC EVALUATION OF HIGH-DOSE METHOTREXATE THERAPY — William Isacoff, UCLA School of Medicine

In clinical and laboratory studies performed during infusions of high dose methotrexate, we have developed an effective protocol which permits such therapy without prohibitive risk to the patients. The pharmacologic data obtained indicate that the rate of drug disappearance from the systemic circulation following these infusions is dose related and that such data are useful in identifying patients who are at risk from serious toxicity. Once guidelines for safe administration were clearly established, an extensive program was undertaken to determine the potential usefulness of high-dose methotrexate therapy in a wide variety of malignant diseases.

After the monitoring of our first 111 infusions, we were able to demonstrate that high doses of MTX could be given to patients without prohibitive risks of toxicity or adverse effect. Once guidelines for the safe administration of HD-MTX were clearly established and well-defined, community private practice-based oncologists as well as other university teaching hospital-based oncologists began entering patients on our protocol. In general, these predictive guidelines have relied on both estimates of renal function prior to and accompanying MTX therapy and the availability of a reproducible and reliable assay for MTX blood determinations which could give us important information about the drug's rate of disappearance from the systemic circulation.

Blood samples for MTX analysis were drawn from patients as defined by the protocol and sent to the Medical Oncology Research Laboratory at Harbor General Hospital in Torrance, Calif. Specimens would usually arrive at our laboratory within 2 hrs after they were obtained from the patient. Within 4 hours, analysis was complete and results phoned to the primary care oncologist. In practice, if samples were obtained from a patient at 8 a.m., results were phoned to the physician by 2 p.m. of the same day. Should blood MTX levels be dangerously high, appropriate rescue intervention was initiated so as to prevent toxicity. As a result of this broad based interaction, several unique precedents in clinical cancer may evolve.

(1) The routine use of pharmacologic data obtained from patients receiving potentially dangerous chemotherapy, proved valuable in therapeutic decision making. This resulted in a marked decrease in toxic manifestations from HD-MTX therapy and hence an increase in therapeutic index.

(2) Once toxicity was easily and well controlled with appropriate rescue maneuvers, the use of MTX in high doses was made available to 20 oncologists at 15 different institutions within Southern California. It soon became clear that with the proper laboratory support this type of phase I and phase II clinical trial could be accomplished at community hospitals by qualified oncologists in private practice. Within a relatively short period of time, over 200 patients were treated with a wide variety of malignant diseases. They received over 500 courses of therapy.

It is necessary to emphasize that the protocol which has been re-

ferred to is potentially dangerous, and has been employed by participating oncologists only under specific clinical circumstances. Written consent was obtained from all patients after being informed as to the investigational nature of the therapy. For each course of therapy, a three day period of hospitalization was required. All patients undergo a thorough pretreatment evaluation before each MTX infusion. Meticulous attention was paid to adequate intravenous hydration and urinary alkalinization prior to each infusion. Monitoring the blood MTX levels following each course of therapy appears to be critical. The successful use of HD-MTX therapy has been possible only by the well coordinated effort of participating physicians, patients and their families, oncology nurse specialists, messengers, laboratory research technicians, protocol clerks and secretaries.

It would ordinarily be expected that such a complex protocol procedure be the undertaking of a specialized cancer center for it to be safe and effective. However, when we compare the results obtained by community-based oncologists to those obtained by university-based oncologists, the number of therapeutic responses or toxic reactions differed little. 40% of the patients were treated in community hospitals and 60% in university hospitals.

COMBINED CHEMOTHERAPY, RADIOTHERAPY AND IMMUNOTHERAPY IN OAT CELL LUNG CANCER – Lawrence Einhorn, Ned Hornback, Indiana Univ. Medical Center

Fifty-eight patients with oat cell lung cancer were treated with a combined modality regimen consisting of chemotherapy, radiotherapy, and immunotherapy. There were 27 (43%) partial remissions and 23 (41%) complete remissions. Eleven patients (19%) remain alive and in complete remission from 53 to 125 weeks.

NEW RESCUES FOR HIGH-DOSE METHOTREXATE – RESPONSES IN OVARIAN AND PROSTATE CANCERS – Isaac Djerassi, Mercy Catholic Medical Center, Philadelphia

High-dose methotrexate-citrovorum factor rescue is a powerful and potentially curative treatment for osteogenic sarcoma and for cancer of the lymphatic system (lymphosarcoma and reticulum cell sarcoma). Its use for control or eradication of other tumors has been limited by the risk of catastrophic toxicity. Citrovorum factor rescue occasionally fails to work and the patient dies in great misery. Really reliable rescue, if available, could lead to new dose-schedules of methotrexate, effective in tumors which do not respond to other drugs or drug combinations.

During the past two years we concentrated on developing systems to insure full safety for this type of treatment. Two approaches were pursued simultaneously:

1. Charcoal filtration of all of the patient's blood in order to remove excess methotrexate and prevent toxicity and

2. Massive dose rescue with citrovorum factor, to arrest without fail methotrexate toxicity when the usual doses of citrovorum fail. Success with the above made possible effective therapeutic trials in ovarian and prostate cancers, previously considered unsuitable for MTX-CF.

An artificial kidney (hemodialysis) to dialize out the excess methotrexate was considered first. Unfortunately this method was efficient only when the MTX concentration in the blood was very high. Its efficiency for trace amounts was very low and could not solve the problem.

We turned therefore to charcoal filters initially developed for removal of barbiturates from overdosed patients. In vitro trials in our laboratory showed that methotrexate, like barbiturates, adheres to charcoal and could thus be removed from the blood. At preselected times after treatment with MTX we attached the patients to a vein to vein extracorporeal circuit. The blood was collected and propulsed mechanically from one vein to another interposing a charcoal filter in its path.

We have so far studied 14 patients on 21 occasions when delay of MTX excretion was leading to life-threatening toxic reactions. Based on previous experience, high mortality is expected in such patients. All patients recovered. The antitumor effects of the methotrexate treatment did not appear to be modified.

Charcoal filtration can reduce the incidence of severe reactions to MTX. The safety of MTX treatments can thus be increased. Higher doses of MTX and more frequent treatments required for affecting previously unresponsive tumors can now be tried.

THERAPY OF HUMAN MALIGNANCY WITH HIGH DOSE METHOTREXATE: CURRENT STATUS REPORT – George Canellos, Sidney Farber Cancer Center

Toxic effects of the drug can be cancelled by the subsequent or coadministration of an antidote compound known as citrovorum factor or leukovorin. The principle dose limiting side effects of methotrexate have been bone marrow suppression and mucous membrane ulceration. Both of these effects can be rescued by the administration of citrovorum factor. The rationale for using high doses of methotrexate is that large concentrations of the drug can be placed in the cell with saturation of all binding sites for the drug when present in excessive amounts. Further high concentrations in the blood would permit more drug diffusion in poorly vascularized solid tumors which has always been a limiting physiologic barrier to effective chemotherapy. In addition, cytotoxic concentrations of the drug can be achieved in the cerebrospinal fluid which would offer a useful means for the treatment or prevention of the central nervous system metastases, especially diseases which have a high predilection for central nervous system metastases such as leukemia, lymphoma, breast cancer and lung cancer. Because the toxic effects of the agent can be rescued, it would permit high dose methotrexate to be included in combination chemotherapy programs composed of drugs which may have other mechanisms of action.

One of the potentially limiting factors in the use of high dose methotrexate has been its propensity to cause secondary renal failure. A review of 143 patients treated with high dose methotrexate ranging from 1 to 7.5 gm/m^2 with citrovorum factor rescue and urinary alkalinization, myelosuppression was noted in only 5.5% of the infusions. Renal toxicity was noted in 15% of the cases. Serum creatinine and serum methotrexate levels can be used to assess the adequacy of drug removal from the plasma 24 hours after initiation of treatment as well as to measure the adequacy of renal function.

Another compound, thymidine, can be used to reverse the effects of methotrexate. Thymidine is converted at the cellular level to the DNA precursor substance, thymidylic acid whose synthesis is inhibited by the action of methotrexate. Thus, thymidine can be used to bypass the metabolic blockade induced by methotrexate.

The use of high dose methotrexate in the adjuvant therapy of osteogenic sarcoma has been previously reported from this institute (Jaffe). Long-term followup of that group of patients in addition to a more recent series where the drug adriamycin was included with methotrexate reveal a consistent disease-free survival after 18 months in the range of 60 to 65% of patients. The disease-free survival curve remains flat beyond 18 months.

High dose methotrexate has been shown to have interesting effects in squamous carcinoma of the head and neck where 82% of the patients had a response. In addition, the use of this agent for the treatment of patients prior to surgery or radiation therapy for advanced lesions of the head and neck has revealed it to be even more effective in that setting with rapid regression of large tumor masses prior to the application of definitive local treatment. This study is currently in progress and is designed to test the efficacy of chemotherapy administered prior to definitive local treatment with a view to decreasing or eliminating the major problem in such patients, namely, local recurrence of disease.

The prospects of eradication of microscopic metastases in other sites is being examined.

DEVELOPMENTS IN TREATMENT OF TESTICULAR CANCER – Robert Golbey, Memorial Sloan-Kettering

Eighty evaluable patients were treated with cis-platinum from July 1975 through September 1976. 63% of those treated attained complete remission and a total of 88% achieved either complete or partial responses. As of Dec. 1976, 63% of the total remained free of evidence of disease.

Our present plans call for revision of the current program to include a somewhat more vigorous consolidation phase of therapy. We are also currently discussing the advisability of randomly using immuno-stimul-

ation in the complete responders to evaluate its possible place in increasing the 'cure' rate.

We will also be embarking on a cooperative study to investigate the usefulness of adjuvant chemotherapy earlier in the course of the disease. There are significant problems with the use of adjuvant therapy which must be clarified before its general use is encouraged.

COMBINATION CHEMOTHERAPY WITH CIS-DIAMMINEDICHLOROPLATINUM, VINBLASTINE, and BLEOMYCIN IN DISSEMINATED TESTICULAR CANCER – Lawrence Einhorn, Indiana Univ. Medical Center

The chemotherapy regimen of platinum + vinblastine + bleomycin produced 74% complete remission and 26% partial remission in 47 evaluable patients; with the addition of surgical removal of residual disease in 5 of the partial remissions, an 85% disease-free status was obtained. Toxicity, although significant during the 12 week remission induction, was usually manageable. Maintenance therapy was well tolerated and all patients returned to work or school full-time.

Thirty-eight of these 47 patients remain alive and 32 remain alive and disease-free 6 to 30 months. The complete remission rate of 74% and overall disease-free status of 85% is as high as has been seen in any adult malignancy treated with chemotherapy.

THE INTERACTION OF DRUG AND RADIATION EFFECTS ON NORMAL TISSUES – Theodore Phillips, Univ. of California Medical Center (San Francisco)

We have developed in our laboratory four new systems for measuring radiation effects through lethality in histologic endpoints in the brain, lung, esophagus, and kidney. Four other systems have been adopted and modified for use in our laboratory and give us a wide range of measurement capabilities. These systems have been applied to the determination of the effect of fractionation and dose rate in radiotherapy and have led to the elucidation of principles of fractionation effect. Particularly important is the detemrination that the effect of fractionation of dose differs for each tissue type. this is the dose level for severe injury and the time of expression of injury. A secondary important finding is the degree of long term repair of radiation injury and the permissible degree of retreatment. These laboratory findings were used to derive formulae for equating time and dose factors in radiotherapy and were tested extensively in the lung and the spinal cord with excellent correlations, allowing prediction of clinically tolerated doses with varying treatment regimens.

More recently, these systems, as well as tumor systems, have been applied to the evaluation of the modification of radiation effects in tumor and normal tissue by drugs. Particular emphasis has been placed on radioprotective compounds and on cancer chemotherapeutic agents. We have discovered that thiophasphate compounds apparently differentially protect normal tissue over tumor. This differential effect is due primarily to the fact that protection occurs only in aerated tissues and, secondarily, to the fact that better perfusion and drug access occurs in normal tissues than in tumors. Direct application to patient care is expected within the coming year. These findings should result in reduced morbidity and increased local tumor control if the animal findings are borne out by clinical trials.

These systems have also been applied to the evaluation of the interaction of radiation and cancer chemotherapeutic drugs. We have found that there are three major classes of drugs in terms of their interaction with radiation. A few antibiotics, such as adriamycin and actinomycin, are strict radiation enhancers or sensitizers and cause the same degree of enhanced response in both tumor and normal tissue. A second category of drugs seems to give significant tumor response enhancement with minimal normal tissue response enhancement at clinical doses. These include BCNU and bleomycin. Cyclophosphamide, because of high cell kill in tumor and little effect on normal tissues, is also in this category.

A third group includes agents which have very little interaction with normal tissue, but as yet have shown only mild enhancement of tumor response as well. These include vincristine, 5-fluorouracil, and methotrexate. The tumor response enhancement may be extremely specific and is not noted in specific mouse tumors currently being studied. These findings have been applied in the design of clinical trials for head and neck cancer and have shown promising results with combinations of bleomycin, cyclophosphamide, adriamycin, and methotrexate. Enhanced normal tissue injury with certain compounds appears to be related to their activity as general sensitizers, as listed above, and to their specific toxicity in certain organs. Thus, enhancement in all organs is seen with actinomycin and adriamycin, in skin and mucus membranes with bleomycin, in heart with adriamycin, in intestine with 5-fluorouracil, etc. These principles have been applied to the review of clinical information and are clearly supported, and have been used to predict the occurence of complications due to interaction of radiation and drugs and to predict factors by which radiation dose must be reduced.

THE USE OF SUBSTANCES THAT MODIFY THE RESPONSE OF TUMORS TO RADIATION TREATMENT – Raul Urtasun, Univ. of Alberta

Improving the results of tumor irradiation has been sought in different ways. One of them, the use of chemicals that sensitize resistant tumor cells to radiation has been employed in pilot investigational projects. Two of these drugs, metronidazole and RO-07-0582, are being investigated. So far, the improvement that has been predicted from extensive laboratory work in animals has been proved to be correct in malignant human brain tumors indicating a significant delay in tumor regrowth, raising hopes that this drug could be employed, in the future, in other tumors presently resistant to radiation.

The toxicity of these drugs of high doses in humans has been assessed, as well as their distribution through the body and into the tumors. These drugs appear to obtain maximum concentration in blood between four and six hours after administration by mouth. Tumor concentrations are reached between five to six hours. Both drugs appear to cross the blood brain barrier and distribute in brain tumors.

The areas that progress is being made in this field presently are in searching for less toxic and more effective drugs; combining these drugs with other types of radiation, more effective than Cobalt gamma rays or x-rays, such as particle radiation (neutrons, carbon ions or pi-mesons); and assessing the cytotoxic effect of these drugs per se, in the hypoxic cells without radiation and with hyperthermia.

HYPERTHERMIA AS A TREATMENT OF SOLID TUMORS – G.M. Hahn, Stanford Univ.

Elevated temperatures (42-45°C) kill mammalian cells without causing immediate cell necrosis. The amount of cell killing is a function of the exact temperature, duration of treatment, and of cell type. Malignant cells appear to be more sensitive to heat than their normal counterparts. Furthermore, hyperthermia sensitizes cells to X-irradiation and to the action of a variety of chemotherapeutic agents. We have made use of these facts to heat transplantable tumors in mice and spontaneous neoplasms in dogs and cats.

Our results show that with some murine tumors cure-rates of 100% can be achieved by single treatments of about 30 min. Damage to normal tissue appears to be minimal. Other mouse tumors, although they regress, are not cured by heat; however heat and chemotherapy given in proper sequence, are frequently effective.

The data obtained in our "large animal" study are also highly encouraging. In animals whose extent of disease is frequently comparable to that in terminal patients, we have achieved complete regression in approximately 15% of the treated tumors. We are currently beginning a phase I study of the technique in selected human patients.

EFFECT OF CYTOTOXIC DRUGS ON ENDOCRINE FUNCTION AND THE VALUE OF ADJUVANT CHEMOTHERAPY IN BREAST CANCER – David Rose, Univ. of Wisconsin

Adjuvant chemotherapy in breast cancer is of greater benefit to the premenopausal than the postmenopausal patient. Our study indicates that this difference may arise because the cytotoxic drugs employed suppress endocrine function, and particularly the secretion of estrogens from the ovaries.

This finding is important clinically because it suggests that some

form of endocrine adjuvant therapy should be included in selected breast cancer patients.

We have found that within 6 months of adjuvant chemotherapy most premenopausal breast cancer patients show a decrease in plasma estrogen and progesterone levels to those usually seen in postmenopausal women. There are reciprocal elevations in plasma LH and FSH, indicating that this abnormality is a direct effect of the drugs on the ovaries. These changes occur with both L-PAM given alone, and a combined drug regimen. In approximately 75% of the women menstruation actually ceases during chemotherapy.

The increases in plasma prolactin after pituitary stimulation are significantly less when the patients have received chemotherapy, but in 4 of 28 cases (14%) there was an exaggerated plasma TSH response.

Adjuvant chemotherapy causes suppression of ovarian activity in premenopausal breast cancer patients ("chemical oophorectomy"); in many cases, there is also inhibition of prolactin secretion. In some patients, adjuvant chemotherapy causes damage to the thyroid gland with resulting hypotheyroidism.

Our results imply that the efficacy of adjuvant chemotherapy may arise largely from its inhibitory effects on endocrine function. A similar hormonal effect can be obtained by another group of less toxic compounds, the antiestrogens.

It is now possible to predict those patients who are likely to benefit from endocrine therapy by measuring an estrogen-binding protein ("estrogen receptor") in the cancer tissue.

The need now is for clinical trials which incorporate the use of an antiestrogen, alone and in combination with cytotoxic drugs. Patients for these treatments would be selected on the basis of the estrogen receptor test.

Our finding that cytotoxic drugs can cause thyroid damage acts as a warning to physicians to look out for this complication. Its importance stems from a report that the prognosis in breast cancer is worsened if patients have a history of hypothyroidism.

INDIVIDUALIZING THERAPY IN BRAIN TUMOR PATIENTS – Paul Kornblith, Harvard

Brain tumor diagnosis and therapy can be improved by the use of tissue culture of individual patients' brain tumors. We have been able to grow tumor cells from 95% of patients undergoing surgery for brain tumors. These cells can be characterized as to their origin by multiple parameters. By careful study, the degree of malignancy of the patient's tumor can be more accurately defined than is possible with conventional approaches. Chemotherapeutic drug regimens can be tested against cultured tumor cells from an individual patient and the responses extrapolated to the clinical situation within six weeks after surgery.

New drugs or combinations of drugs can be evaluated by this technique for their applicability to the therapy of a specific patient. Radiation effects against individual patients' tumor cells can be now studied and approaches altered in those cases in which there is minimal response to the radiation. The complex variables in the host immune response can be evaluated on a patient by patient basis and an understanding of this potentially useful antitumor defense mechanism achieved. Use of the immunological study of antibody response has had the additional value of serving as an adjunct in the diagnosis of brain tumors.

Thus, although there is an overwhelmingly difficult problem yet to face in the area of brain tumors, we have now developed approaches and valuable tools to help us tackle this problem.

QUANTITATIVE DECISIONMAKING IN CANCER DIAGNOSIS AND TREATMENT – Thomas Lincoln, Rand Corp.

The organized approach to cancer diagnosis and treatment is undergoing a quiet revolution based on a combination of quantitative laboratory measurements, computer technology, and methematical analysis. The results will be a new level of precision in diagnosis and patient specific therapy. In part these results have already begun to appear.

Our research group is concerned with all aspects of this revolution: (1) The development of mathematical models which describe the distribution of chemotherapeutic drugs so that the concentration of a drug canbe predicted at the site of action and so that the concentration can be manipulated to improve results and avoid toxicity. (2) The inclusion of physiologic information so that individual physiological differences can be taken into account. (3) The linkage of such models to laboratory data and patient data. (4) The organization of decision procedures based on this quantitative base and (5) the statistical evaluation of the results.

This approach is of practical importance in deriving the best results from what we have learned through research so that it may be applied to the treatment of individual patients.

We are using four major approaches aimed at an increased quantification and precision in the diagnosis and treatment of cancer:

1) Mathematical models to describe the proliferation of cancer cells and normal cells. These models are designed to identify biological differences in cell behavior which can be used to predict how certain chemotherapeutic agents act, and to improve the strategies for their administration.

2) Mathematical models of drug distribution which accurately reflect the exposure of cells and tissues to a particular chemotherapeutic agent.

3) The statistical analysis of patient specific risk factors, to improve our ability to choose among alternative types of therapy.

4) The analysis of data related to the functions and activities of cells in the immune system so as to more accurately characterize the biological behavior of the leukemias and the lymphomas.

CONTRACT AWARDS

Title: Adjuvant trials in resectable non-oat cell lung cancer
Contractor: M.D. Anderson Hospital, $487,446; and Ontario Cancer Institute, $485,570.

Title: Continuation of administrative support services for Eastern Cooperative Oncology Group
Contractor: Georgetown Univ., $175,314.

Title: Continue studies of type C tumor viruses
Contractor: Microbiological Associates, $224,959.

Title: Continue research on spontaneous and virus induced neoplastic formation
Contractor: Meloy Laboratories, $654,968.

Title: Conduct a study of the occupational cancer risk in Hawaii
Contractor: Univ. of Hawaii, $137,513.

Title: Conduct research on the epidemiology of primary liver cancer in selected counties in Texas
Contractor: Univ. of Texas Medical Center, Galveston, $222,818.

SOLE SOURCE NEGOTIATIONS

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

Title: Immunologic study of RNA (type C) viruses
Contractor: Scripps Clinic & Research Foundation.

The Cancer Letter—*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.