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TWO MORE TREATMENT PROGRAMS MOVED TO DCT; RAUSCHER PONDERS FATE OF COOPERATIVE GROUPS

The controversy raging inside NCI over control of treatment research programs has resulted in two more bitterly-contested branch transfers and could bring about an even more traumatic shakeup involving the cooperative clinical groups.

The Surgery Branch and the Radiation Oncology Branch, both in the Div. of Cancer Biology & Diagnosis, have been transferred to the Div. of Cancer Treatment. DB&D previously had lost the clinical research director to DCT.

The branch chiefs Steven Rosenberg of surgery and Ralph Johnson of radiation oncology will go with the move to DCT. George Canellos had previously been named clinical director when that position was moved to DCT.

The decision by NCI Director Frank Rauscher to make the move was

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In Brief

UNSOLICITED PROPOSALS "VERY VALUABLE," DEVITA SAYS, ASKS INVESTIGATORS TO KEEP CHANNEL OPEN

UNSOLICITED CONTRACT proposals "are very important to the Div. of Cancer Treatment," Vincent DeVita, director of the division, told the DCT Board of Scientific Counselors. "It is very valuable to us, to receive a lot of unsolicited ideas, to keep this channel open." . . . **CYCLAMATE BAN** should be lifted, according to a petition by Abbott Labs to FDA, based on 26 studies in both animals and humans which failed to develop any evidence of carcinogenic potential in the compound. The studies cited by Abbott include one supported by NCI on cyclamate and saccharin, by F. Homburger, and a recent World Health Organization report on food additives which said flatly, "It is now possible to conclude that cyclamate has been demonstrated to be non-carcinogenic in a variety of species." . . . **NAME CHANGE**: The National Institute of Neurological Diseases & Stroke at NIH is now the National Institute of Neurological & Communicative Disorders & Stroke . . . . **MEETINGS** to watch for in May: Cooperative Clinical Trials Group "Potomac Conference," May 22-24 at NCI, with possible changes in the program's direction, management, and mission as official and unofficial topics; Molecular Control Working Group, May 28 at NCI, to discuss applications of molecular biology to the design of antineoplastic drugs; and the Subcommittee on Centers, May 21 at NCI, to continue the review and evaluation of the cancer centers program and recommendations to the National Cancer Advisory Board. . . . **PUBLICATIONS**: "National Cancer Program, Report of the Director," HEW Publication NIH-75-472, an illustrated copy of Rauscher's annual report to the President – write to NCI, Cancer Communications, Bethesda, Md. 22014.

DCT WINNING STRUGGLE FOR CONTROL OF SCATTERED TREATMENT PROGRAMS

(Continued from page 1)

a resounding victory for DCT forces headed by the division's deputy director, Stephen Carter. Last year, more than a year after the division's responsibilities had been expanded from chemotherapy to nominally include all treatment research, Carter and the now-retired DCT Director Gordon Zubrod expressed frustrations over their inability to influence treatment programs administered by other divisions. Carter publicly criticized the situation in a paper he presented at a meeting of the division's advisory committee (now reorganized into the DCT Board of Scientific Counselors).

Fighting for the status quo was Nathaniel Berlin, DB&D director until he left April 1 to head Northwestern's cancer center. Berlin lobbied relentlessly to keep his treatment programs, but the handwriting was on the wall when Rauscher named Canellos clinical director and took that key position away from Berlin.

Vincent DeVita, who took over DCT when Zubrod retired to become director of the Miami Comprehensive Cancer Center, stayed out of the fight, publicly at least. But he welcomes the changes and fully intends to take charge of as many treatment programs as Rauscher will give him.

One of those he doesn't have yet is the $20 million a year cooperative clinical group program administered by the Div. of Research Resources & Centers. All grant programs, except for the new one in the Div. of Cancer Control & Rehabilitation, come out of DRR&C which was formerly the Div. of Research Grants. DRR&C attempts to coordinate its programs with those of other divisions with exchange of information and liaison personnel.

It's a much more difficult problem with the widely scattered and highly independent cooperative groups. Their friends at NCI insist the program has been very effective in testing new drugs and treatment regimens. But Carter and others chafe at lack of coordination with other NCI treatment efforts and their inability sometimes to find out what the cooperative groups are doing.

DeVita told his Board of Scientific Counselors that "the cooperative groups are a big problem. With a great deal of effort we can communicate with but not cooperate with them. . . I don't think we should integrate to the point where we stifle new ideas, but clearly in some areas we are not getting the most for our efforts."

Rauscher has agonized over the entire problem for more than a year and has said it has caused him more headaches than any other aspect of his job. His worst headache is developing now, over what to do about the cooperative groups. He is known to be leaning toward at least requiring them to report to DeVita, if not transfer them entirely into DCT.

That decision could have broader implications. A strong element at NCI feels that it is ridiculous for grant programs to be administered by DRR&C independently of what other divisions are doing in the same areas either in-house or through contracts.

"A grant is merely a funding mechanism," a senior NCI executive told *The Cancer Letter.* "It doesn't make sense to limit grants to a division that has no program responsibility. Grants and contracts should be available to all divisions."

Much of the grant program funded through DRR&C involves basic research which might not fit clearly into one of the other divisions. But a major portion of it, including a wide range of basic research, appears to mirror programs in the other divisions drug development, viral oncology, carcinogenesis, immunology, radiation therapy, chemotherapy, tumor biology, diagnostic research, epidemiology.

If the reorganization of treatment activities is carried out to what some feel is its logical conclusion, most of the grant programs would be handed over to other divisions, perhaps leaving DRR&C with only the cancer centers as its major responsibility.

A further ramification of the move of the clinical director to DCT is that it made the job of associate director for medical oncology in DCT somewhat superfluous. DeVita told the Board of Scientific Counselors last week that he was planning to abolish that position and merge it with that of the clinical director. Such a move requires approval of NIH, which has not yet been granted.

Paul Carbonne, who had been associate director for medical oncology, is now special assistant to DB&D Director Alan Rabson.

DRUG DEVELOPMENT EFFORT CRITICIZED; DEVITA AGREES TO "TAKE A LOOK AT IT"

The Div. of Cancer Treatment is in for some intensive scrutiny itself as the result of criticism by members of the Board of Scientific Counselors aimed at the division's heretofore sacrosanct drug research and development program.

The program was started about 10 years ago by Zubrod and was his pride and joy; in fact, it was the major activity of the division when it was known as the Div. of Chemotherapy.

The $30 million a year program includes a massive screening effort to find compounds with antitumor activity. It has screened more than 400,000 compounds.

So far, that effort has resulted in the discovery of only three new classes of drugs effective against cancer—DTIC, the nitrosoureas (with three separate drugs), and hexamethylmelamine.

Four other compounds with anticancer activity were discovered by others but developed by the NCI

program – L-asparaginase, hydroxyurea, mithramycine and ara-C.

"What are you achieving?" asked John Ultmann, board member from the Univ. of Chicago. "The achievement is not in proportion to the money spent. You're not getting your money's worth. . . [The drug screening program] is a beautiful system, a well-oiled piece of machinery; but you've got to re-examine the machine. I must question whether or not you should recycle some of the $30 million to brilliant individuals, and just leave them alone."

Saul Schepartz, who heads the drug R&D program, pointed out that NCI has a five-year contract, at $25 million a year, with the Southern Research Institute which does just that, permitting a great degree of investigator freedom.

But DeVita said to Ultmann, "I agree 100% with you. We must examine the program. I'm not sure that there's a better system, but we're taking a long, hard look at it. . . My view is that, with only three compounds coming out of the program in all these years, it is not a good record. However, there are many in clinical trials (not originally found in the NCI screen) that probably wouldn't be there without this program."

Philip Rubin, board member from the Univ. of Rochester, suggested that "you are getting so good at identifying new drugs, following those leads could absorb all your resources without producing effective new drugs."

"We should take a chance we will miss a good cancer agent in the next 35,000 screens, and put our money on improving what we've got," Ultmann said. "Put your money where your chips are. Stand up to Congress if necessary. Tell them, we've got 45-50 drugs and we will concentrate on those."

Again, DeVita agreed. "We cannot continue random screening of all compounds. We must make it more rational. We should ask the question, is screening valid? We cannot continue to chase on a random basis every compound that comes into the world. It absorbs too many resources that could be used more productively."

DeVita pointed out that "we were formerly a drug development organization. Our mission now is different. Our skills were primarily in drug therapy. We're trying very hard to change that."

MORE EXCERPTS FROM PAPERS PRESENTED AT ACS WRITERS SEMINAR

Excerpts from presentations made to science writers at a seminar sponsored by the American Cancer Society appear on the following pages, and are continued from last week. Some of the material has been previously published, some of it includes preliminary data from ongoing studies.

ACS has a limited number of copies of most of these papers and will send them upon written request as long as they last. Write to ACS, Alan Davis, vice president science writer, 219 E. 42nd St., NYC, 10017.

ANTITUMOR EFFECTS IN MAN WITH IN VITRO PRODUCED LYMPHOKINES – *Edmund Klein, Roswell Park*

Lymphokines, substances produced by lymphocytes in vivo and in vitro, were recently shown by us to have antitumor effects in human cancer. Injections of lymphokines into malignant lesions were followed by tumor regressions. The neoplastic lesions under study included breast cancer, lymphomas involving the skin (reticulum cell sarcoma, mycosis fungoides), basal cell carcinoma and squamous cell carcinoma. Regressions were almost entirely limited to treated lesions and varied from partial to complete.

Initially, lymphokine preparations were available only in such minute amounts that effective clinical investigation was virtually impossible. Methods were recently developed to obtain lymphokine preparations in large quantities from concentrated fresh human lymphocytes or human lymphocytes growing in tissue culture. These sources make possible the systemic exploration of lymphokines for the control of widespread cancer. If this approach to immuno therapy appears warranted, the large scale availability of lymphokines for clinical use is practical.

BACTERIAL SENSING AS A MODEL FOR HIGHER SENSING SYSTEMS – *D.E. Koshland Jr., Univ. of California (Berkeley)*

The study of bacterial sensing shows that bacteria make choices, can discriminate between closely similar chemicals, have a rudimentary "memory," and can make judgmental decisions. Analysis of the systems at a molecular level show that they are very similar to, and hence may be good models for, higher sensory systems.

The bacterial sensing has a formal "engineering" analogy to higher systems. The receptors are located on the surface of the bacteria as are the organs of taste, smell, and sight in higher species. The transmission system is common to many receptors, as is the central nervous system of vertebrates. The motor apparatus is activated by command of the transmission system in analogy to our arms and legs. The bacterial system has a great advantage for study over higher systems, however, in that it is relatively simple and bacteria can be manipulated chemically and genetically with relative ease and without legal complications.

CAFFEINE: A MODIFIER OF THE ACTIVITY OF CARCINOGENS AND ITS INCORPORATION INTO GENETIC MATERIAL (DNA) – *J.E. Cleaver, Univ. of California (San Francisco)*

Many chemicals are known which are innocuous themselves, but can increase or decrease the numbers of mutations and cancers caused by other agents.

Caffeine is one of these chemicals which is important because of the size of the human population exposed to it on a regular basis. One can make an approximate estimate that heavy or continual coffee drinking produces a maximum concentration of about 10 micrograms per ml in the body; the effects of caffeine on mutagenesis and carcinogenesis mentioned above occur at concentrations of up to 100 to 200 micrograms per ml. Cells from patients with xeroderma pigmentosum (XP), however, are more sensitive than normal human cells to some of the effects of caffeine.

Caffeine is known to interfere with a DNA repair process, and it increases carcinogenesis in some laboratory experiments (chemical carcinogenesis of hamster cells) but decreases carcinogenesis in others (ultraviolet light induced skin cancer in rabbits).

The reasons for these effects is not known at present, and we have begun to study the ways caffeine is altered in human cells because surprisingly little is currently known. Until recently all theories of how caffeine works were based on the assumption that caffeine enters cells and acts by binding to regions of damaged DNA or inhibiting enzymes that may be associated with DNA repair processes. We find, however, that caffeine is rapidly and completely converted into compounds which can enter DNA. These compounds are thymine, adenine, and guanine. High concentrations of these compounds are known to be toxic to cells. Consequently we think that caffeine can disturb synthesis of DNA, especially in cells already damaged by radiation or carcinogens, by acting as an unusual source of large and unbalanced amounts of precursors of DNA which can block action of some of the enzymes which repair DNA.

ADVANCED CHILDHOOD LYMPHOSARCOMA AND RETICULUM CELL SARCOMA (NON-HODGKIN'S LYMPHOMAS) — 5 YEAR "CURES" AFTER TREATMENT WITH METHOTREXATE–CITROVORUM FACTOR RESCUE — ***Isaac Djerassi, Mercy Catholic Medical Center (Philadelphia)***

In 1968 I reported briefly that the new treatment method with pulse methotrexate and citrovorum factor rescue we were studying in acute leukemia, caused remarkable reductions of tumor masses in children with lymphomas. These observations were interesting since methotrexate used in any other manner was and still is totally ineffective in this type of cancer.

The first 10 patients we treated with methotrexate-citrovorum factor rescue in a phase I study were terminal and beyond salvaging. All showed substantial tumor regressions. In the course of these efforts, we developed an optimal dose-schedule and a system for the use of methotrexate-citrovorum in lymphomas which was then applied to 12 new patients with lymphomas not treated previously with other drugs. *Six of these 12 patients (50%) are alive and well today*, 2½ to 5 years after stopping the methotrexate treatment, 2½ to 4½ years after stopping all treatment, and 5 to 8½ years after diagnosis. Five of these 6 patients had advanced, generalized lymphoma with a very short life expectancy. . . .

With this report and the presentations of these results to the medical profession, non-Hodgkin's lymphomas (lymphosarcoma and reticulum cell sarcoma) are joining this year the list of human cancers in which 5 year "cures" have been achieved, where none were possible before. This and the steady flow of progress, basic and clinical, in the cancer field, should encourage researchers, public and politicians alike. We have all been witnessing in awe, practically every year, a new type of cancer, coming for the first time since the creation of the species, under good, or permanent control.

Ten years ago, curing one acute leukemia patient or one stage IV lymphoma would have been an act of God. Today it is an act of Congress.

AN ETIOLOGICAL HYPOTHESIS FOR BREAST CANCER — ***Brian Henderson, Univ. of Southern California***

Several risk factors have been associated with breast cancer. Some of these, earlier age at menarche, delayed age at first pregnancy and menopause and decreased risk following premenopausal oopherectomy have suggested an underlying hormonal abnormality of ovarian or pituitary origin. The nature of this abnormality has been the subject of considerable investigation.

Several investigators have focused on the relative amounts of the three estrogen fractions. Two of the fractions (estradiol and estrone) regularly produce mammary tumors in rats while the third (estriol) apparently does not. This suggested that estriol may be an antogonist of the other two fractions by competing for binding sites in breast tissue. Other hormonal hypotheses based on animal experiments have suggested a role for prolactin, progesterone and adrenal steroids. Studies of human breast cancer cases have not yet clearly defined the role of any of these hormones in the etiology of breast cancer.

Our previous study indicated that certain risk factors found in women with breast cancer could also be found in their mothers. We have subsequently found that sisters of breast cancer cases have a decreased age at menarche, increased age at first delivery and decreased parity similar to the cases. We reasoned that these findings in the mothers and sisters of breast cancer cases indicated that they shared the same underlying hormonal abnormality. We could not distinguish between a genetic or environmental origin for this familial pattern of hormone excretion.

Assuming that the daughters of breast cancer cases would have the same abnormality as their mothers we have studied in detail the hormone excretion of teenage offspring of breast cancer cases and controls. More of the case daughters excrete elevated levels of estrogen (estrone and estradiol). Preliminary data also

indicate that the case daughters excrete slightly more prolactin and progesterone.

Thus, daughters of breast cancer cases excrete excessive quantities of at least estrogen, prolactin and progesterone. We hypthesize that this hyperexcretion of the pituitary-gonadal axis results from an increased setting of the "gonadostat". Other workers have suggested that onset of menarche is linked to achievement of a critical weight and that girls with an early age at menarche often have an excessive proportion of body fat. This excess body fat may determine a higher setting of the gonadostat.

Further study of hormone excretion patterns in daughters of breast cancer cases should provide needed confirmation of these findings. Pituitary-gonadal hyperexcretion could be controlled by exogenous hormones and possibly diet. Detection of at-risk daughters in their teenage years might provide a valuable means of reducing the incidence of breast cancer.

PAYMENTS TO HOSPITALS FOR THE CARE OF CANCER PATIENTS — ***Joseph Scotto and Sidney J. Cutler, NCI***

Information on hospitalization costs for cancer patients was collected on a ten percent sample of patients in the Third National Cancer Survey. This report is based on information obtained for 3151 patients diagnosed in 1969 and followed for 24 months.

Within two years of diagnosis, the average cancer patient spent 26 days in hospital at a cost of $2,289; 1 out of 8 patients occupied a hospital bed for 50 days or longer. Medicare paid for 41 percent of total payments, Blue Cross insurance, 22 percent; other private insurance, 18 percent; other sources, 6 percent.

Highest hospitalization costs were reported for stomach cancer ($3,269); the lowest, for in situ carcinoma of the uterine cervix ($956). On a daily basis, costs varied from a high of $95 for leukemia to a low of $74 for melanoma of the skin.

AREAS OF PROGRESS IN THE TREATMENT OF CANCER IN CHILDREN — ***J.R. Wilbur, Children's Hospital at Stanford***

Our current state of knowledge and skills is such that in the best cancer treatment centers it is possible to successfully treat and apparently eradicate cancer in at least 50% of all children who come for treatment. The results of treatment of individual tumor types reported recently from major cancer treatment centers include the following survival rates: Acute lymphoblastic leukemia, approximately 50%, 5-year survival. Wilms' tumor, greater than 50%, 5-year survival. Soft tissue carcinomas, greater than 50%, 5-year survival. Osteosarcoma, greater than 50% of the patients doing well without disease at 2½ to 4 years after initiation of treatment. Ewing's sarcoma, greater than 50% survival without evidence of disease to date. Hodgkin's disease, 89%, 5-year survival. Non-Hodgkin's lymphoma, the vast majority of patients doing well without evidence of disease after intensive combination therapy. Ovarian tumors, over 75% continue to do well 4 or more years after initiation of treatment. Brain tumors and neuroblastoma represent the only frequently occurring childhood tumors where the results do not approach 50% prolonged, disease-free survival. . . .

A major interest within our group at the Children's Hospital at Stanford has been to look at ways of improving the team approach and the philosophy of therapy which will result in not only better eradication of disease, but will also contribute to the return of the patient and his family to as normal a life style as possible as quickly as possible. In order to achieve this, it is vital that the patient and his family have a full understanding and involvement in the problem and the plan to solve it. No matter what type of tumor nor how extensive it is, the patient and his family should have a full understanding of the situation and participate actively in the discussions about therapy.

The therapy plan should be directed towards the eradication of the disease. The treatment should be given with the expectation that the patient is going to do well unless proven otherwise. If the tumor is one in which therapy has routinely failed in the past, then some new type of therapy must be devised and utilized in an attempt to eradicate the disease. Everyone on the treatment team, including the patient and his family, should be directing their efforts toward the achievement of this end. The patient should have an understanding of his disease, the therapy plan and the steps being taken to eradicate the disease. Siblings should also be allowed to participate as team members to contribute in whatever way they can to the achievement of this common goal.

SOME INTERESTING FINDINGS OF VIRUSES IN FISH, ESPECIALLY IN THEIR TUMOR-LIKE LESIONS — ***William Dolowy, Chicago Medical School***

In previous surveys of the incidence of tumors in fish, Eric Brown of the Chicago Medical School reported a higher incidence of tumors in fish taken from the Fox River in Illinois, than from less polluted areas such as Lake of the Woods, Ontario, Canada.

Brown also showed a strong positive correlation between 1) an elevated level of a series of chemicals suspected of being natural or industrial and domestic pollutants, and 2) a higher bacterial pollutant count in the Fox River than in the clearer Canadian lake, with 3) the incidence of tumors in fish.

When I joined Dr. Brown about a year ago we began to work with some of the fish he had collected and frozen from the Fox River, Illinois and others from Ontario, Canada, and some fresh fish from a special Environmental Protection Agency project in Wyoming, Michigan, in which fish were experiment-

ally being raised on human sewage as their food source.

The interesting findings that we have demonstrated include:

1) The isolation of human polio-1 virus from a tumor of a catfish from the Fox River in Illinois.

2) The isolation of human polio-1 virus from at least three groups of fish fed human sewage, even though the sewage was treated with potent disinfectants. Two groups of fish whose sewage food had been treated by other disinfection methods did not have viable polio virus.

3) We conducted a number of preliminary attempts to ascertain whether fish were passive carriers of polio-1 or whether the virus was actively growing, i.e., replicating in fish cells; in other words, are the fish "swimming virus factories."

4) In a Canadian fish (Walleye pike) a tumor-like lesion of the skin, known to be caused by viral infection, was studied in great detail by electronmicroscopy.

ADVANCES IN THE CHEMOTHERAPY OF OSTEOGENIC SARCOMA — ***Norman Jaffe, Emil Frei III, Demetrius Traggis, Sidney Farber Cancer Center, Boston***

Osteogenic sarcoma is fatal in 4 out of 5 patients. Death is generally due to the development of pulmonary metastases which appear within 6 to 9 months despite radical primary treatment. The majority of patients do not demonstrate clinical metastases at diagnosis. This suggests that pulmonary micro-metastases are already established at presentation. Studies have demonstrated that high-dose methotrexate followed by citrovorum factor ("citrovorum rescue") (MTX • CF) and adriamycin are effective in the treatment of metastatic osteogenic sarcoma. This prompted the early administration of these agents to newly diagnosed patients following definitive primary treatment in an attempt to destroy the micro-metastases. Preliminary results at the Sidney Farber Cancer Center suggest that such chemotherapy has been successful and has changed the natural history of the tumor by preventing the development of overt disease.

During the past year additional studies have been conducted at the Sidney Farber Cancer Center with a view to more effective therapeutic application of these drugs. The studies were based on an analysis of the action of the drugs on cell cycle kinetics and characterization of the results according to the schedule of administration. Investigations were facilitated by the availability of supportive measures to counteract the possible development of host toxicity and studies to monitor the clinical pharmacology of methotrexate. The experiences of the past 12 months form the basis of this communication.

The original high-dose methotrexate program developed by Djerassi called for the administration of massive doses of methotrexate by the intravenous route over 6 hours. Two hours later, citrovorum factor, which counteracts the effects of methotrexate, is administered for 72 hours. Such treatment courses were administered at 3-weekly intervals for 2 years. The efficacy of the original treatment program was also enhanced by administering vincristine one-half hour before the methotrexate infusion. (A Kodachrome slide to demonstrate the method of treatment is available.)

Relapse or failure of response may be ascribed to inherent cell resistance or emergence of cell resistant lines. We attempted to surmount this problem by increasing the frequency of drug treatment. Thus, the tri-weekly administrations of methotrexate were altered to a weekly schedule in patients who were apparently resistant to methotrexate or other forms of chemotherapy. This therapeutic endeavor resulted in one complete response and three partial responses in seven patients with pulmonary metastases previously resistant to prior treatment. In one of the cases, where only partial regression of tumor was achieved, surgical intervention permitted complete tumor eradication. This altered the patient's status from one of palliation to "potentially curative."

The concept underlying adjuvant treatment is based on the premise that the chances of achieving tumor eradication by effective agents are enhanced when the tumor cell burden is small. This is the basis for administering chemotherapy to destroy pulmonary micro-metastases after removal of the primary tumor. Our preliminary results have demonstrated that over 70% of patients treated with MTX • CF under these circumstances have remained free of pulmonary metastases for 10 to 32 months with a median of 14 months. When compared to an historical control group, this is highly significant.

THE STANFORD MEDICAL PION GENERATOR: A CLINICALLY DEDICATED TREATMENT SYSTEM — ***Malcolm Bagshaw, Stanford***

This is a progress report on the development of a totally integrated and clinically dedicated system for the treatment of patients with cancer, with negative pi mesons. It is anticipated that when completed, the system will be economically feasible, and compatible with installation in major cancer centers.

The pi meson, or pion, is a nuclear particle which is liberated from the nucleus of a target atom on bombardment with other high energy particles, such as electrons or protons. The pion is released from the target in all directions and at different momenta. It is 273 times the mass of an electron, but contains a single negative charge identical to that of an electron. As the pion enters tissue, it is relatively non-destructive to the tissue through which it passes. At the end of its flight, however, it is captured by the nucleus of an atom within the tissue, and produces disintegration of this nucleus.

Products of the disintegration include neutrons, alpha particles, and other relatively heavy nuclear

fragments. In addition, gamma rays are also produced. The alpha particles and other heavier nuclear fragments have a short range within tissue, and very high ionizing potential. Therefore, the pion, a relatively non-destructive particle, may travel through normal tissue and if properly directed, come to rest within a cancer cell where the by-products of its absorption process, by virtue of their capacity for dense ionization, become lethal to that cell. At the same time, gamma rays are produced which may be detected by appropriate radiation detectors placed outside of the body which, in turn, could be used to reconstruct the anatomical site of this densely ionizing process.

MALIGNANT AND NONMALIGNANT CHANGES IN THE HUMAN FEMALE REPRODUCTIVE TRACT FOLLOWING INTRAUTERINE DES EXPOSURE – ***Arthur Herbst, Harvard***

A type of vaginal and cervical cancer called clear-cell adenocarcinoma has been occurring in young females more frequently in the United States and abroad in recent years, associated with maternal ingestion of diethylstilbestrol (DES) and chemically similar compounds. In spite of the increasing number of cases, the cancers fortunately continue to be rare among DES-exposed females.

In contrast, nonmalignant tissue changes in the surface lining of the vagina and cervix are common. These include vaginal adenosis (the presence of glandular tissue in the vagina), cervical erosion or ectropion (the presence of glandular tissue on the cervix), and transverse vaginal and cervical fibrous ridges. The relationship of these changes to the pattern of maternal drug administration will be discussed.

The importance of screening examinations of the post-menarchal exposed population will be emphasized, especially until greater knowledge has been acquired regarding the natural history of these tissue changes.

THE SEROLOGIC DIAGNOSIS OF MEDULLARY CARCINOMA OF THE THYROID ***Kenneth Melvin, Univ. of Oregon***

Thirteen year old identical twin girls were operated on for medullary carcinoma of the thyroid at St. Vincent Hospital, Portland, in December, 1974. Both were found at surgery to have two cancers within their thyroid gland. The disease was in its early stage and was totally excised. The early diagnosis and surgical cure was made possible only through the application of a simple blood test, specific to medullary thyroid carcinoma. This test, involving the measurement of serum levels of the hormone, Calcitonin, has evolved from an extensive research program into the hormonal activities of medullary carcinoma, and represents an excellent example of the principle of early cancer detection through measurement of circulating tumor specific substances.

In neither twin was the cancer detectable clinically or by orthodox diagnostic measures. The diagnosis was predicted, and surgery undertaken, on the basis of the blood test alone. The girls were tested in the first place because their father, and some 20 of his blood relatives, were known to have the disease, which is inherited as a Mendelian dominant trait.

In this kindred, and several others affected like it throughout the USA and abroad, the calcitonin test is proving to be a reliable means of screening for early, occult medullary thyroid cancer, permitting early diagnosis and surgical cure.

BIOMEDICAL PION PROGRAM ***Morton Kligerman, Univ. of New Mexico***

Negative pi mesons (pions) have theoretical advantages in cancer radiation therapy, not only over conventional low LET radiation, but over other forms of high-LET radiation, because they cause a greater concentration of ionization in the tumor. Since February 1974 pions have been produced in the Biomedical Channel at the Los Alamos Meson Physics Facility. Scientists at the University of New Mexico Cancer Research and Treatment Center in Albuquerque and at the Los Alamos Scientific Laboratory have been making measurements and studying the effects of these pions on physical cell cultures, animal tumors and human skin nodules.

Additional papers presented at the American Cancer Society science writers seminar will be excerpted in future issues of ***The Cancer Letter.***

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-CM-67011

Title: *Clinical data retrieval services*
Deadline: *Early May*

NCI's Medical Oncology Branch in the Div. of Cancer Treatment is seeking proposals from qualified sources for clinical data recording and retrieval services. These services will include the development and maintenance of computer systems, the abstraction of data from medical records, the computerization and processing of the data, the monitoring of data due in from medical personnel and contractors, the preparation of data retrievals, summaries and analysis and the randomization of patients.

The services will be performed at a government

facility on the NIH campus in Bethesda, Md., and will involve the use of an IBM 360-370/65 system; 4 data abstractors, 3 of which should be registered nurses; and one data technician who is adept at key-punching, terminal data entry, the use of text editors and general data processing procedures.

Requests for proposals will be available on or after April 30, 1975.

Contract Specialist: Joseph Kerner
Cancer Treatment
301-427-7463

RFP NCI-CM-67010-18

Title: *Therapy of patients with brain tumors*
Deadline: *June 16*

The Div. of Cancer Treatment will make available to interested institutions an RFP to conduct studies of intensive multidisciplinary therapy of patients with malignant gliomas and other types of intracranial tumors, and to determine the efficacy of a number of therapeutic approaches.

Data obtained during the course of this study could provide information on the possible intrarelationships between tumor morphology, extent and clinical stage of the disease, changes in roentgenographic findings, alterations in nuclear imaging, and pharmacatoxicology of selected agents.

A minimum of 35 evaluable patients, having a microscopically confirmed diagnosis of malignant glioma, shall be required each year. A minimum of 20 newly operated (first craniotomy) patients will be randomized each year to the Phase III study and 15 patients with recurrent gliomas into a Phase II study. Each institution should have the overal logistical mobility for conforming to the protocol requirements.

Contract Specialist: Michael Del Colle
Cancer Treatment
301-427-7463

Contract Awards

LITTON BIONETICS FREDERICK AWARDS MORE THAN $16 MILLION THIS YEAR

Recent modifications to NCI's contract with Litton Bionetics for operation of the Frederick Cancer Research Center have brought the total for the year ending in June to $16,038,504. It is the largest contract amount ever awarded by an NIH agency for one year.

One addition to the contract was for $2.2 million for construction and alterations required to implement the basic research program and for subtasks in the viral oncology research area. Another modification added 12 tasks involving alteration and construction totalling $497,000.

Other contract awards included:

Title: Studies related to the therapy of patients with bronchogenic carcinoma
Contractor: M.D. Anderson, $280,636.

Title: Maintenance of rodent production center in modified conventional environment
Contractors: Charles River Breeding Laboratories, $615,611; Southern Animal Farms, $405,928; ARS/Sprague-Dawley, $647,216; Laboratory Supply Co., $391,432, and Simonsen Laboratories, $673,974.

Title: Quantitative evaluation of protected environments
Contractor: M.D. Anderson, $550,000.

Title: Preparation of commercial unobtainable compounds
Contractor: Merck & Co., $94,386.

Title: Administrative and technical support services
Contractor: Automation Industries, Inc. Vitro Laboratories Div., $68,603.

Title: Selection and propagation of sematic cells having specific physiological mutations
Contractor: Univ. of California (San Francisco), $225,870.

SOLE SOURCE NEGOTIATIONS

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

Title: Isolating Type C virus from cultured human leukemic cells
Contractor: Sidney Farber Cancer Center.

Title: Study and production of avian tumor viruses
Contractor: Life Sciences, Inc., St. Petersburg, Fla.

Title: Immunological studies on the relationship of embryonic antigens to virus-induced tumor antigens
Contractor: Duke Univ.

Title: Developmental planning for cancer control pathology reference centers
Contractor: American Society of Clinical Pathology

Title: Cellular immunity studies to herpes simplex associated antigens in cancer patients and controls
Contractor: Johns Hopkins Univ.

Title: Installation and implementation of a chemical information processing system
Contractor: Univ. of Pennsylvania.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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