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GAO CRITICIZES DISTRIBUTION OF COMPREHENSIVE CANCER CENTERS, CITES NEED FOR "FOCAL POINT" CLARIFICATION

The General Accounting Office, the agency established by Congress to help it watch over the Executive Branch, has recommended after completing investigation of the Comprehensive Cancer Centers Program that NCI should:

- Decide on the specific factors that will be used to determine locations of new comprehensive cancer centers, balancing the need for geographic distribution with other factors.
- Report to the appropriate congressional committees on the effect other factors will have on locations of centers and the feasibility of achieving an appropriate geographic distribution.
- Clarify the role of the comprehensive center as a focal point for dem-

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In Brief

NCI TO SUPPLY MAYTANSINE FOR SEVERAL PHASE I STUDIES; HOLLEB URGES REFERRALS TO "EXPERTS"

MAYTANSINE PHASE I tests by NCI at the NIH Clinical Center so far have involved six patients. Only toxic effect observed to date is a lowering of the platelet count in three of the patients. NCI reports tremendous interest in the new drug, with inquiries on its availability from scores of investigators. Franco Muggia, who heads the Cancer Therapy Evaluation Program, said NCI will supply the drug for phase I studies elsewhere but hasn't determined yet how many. Those interested should contact Milan Slavik, chief of the Investigational Drug Branch. Phone 301-496-1196. Other new drugs available for study include chlorozotocin, ledacrin, and diazauridine. NCI is ready to file an IND for diazauridine and will support four to five phase I studies on it. . . . **MEMPHIS REGIONAL** Cancer Center has established a Regional Advisory Committee to oversee and advise on its activities. The committee includes representatives of the center, St. Jude Children's Research Hospital, Univ. of Tennessee, and Baptist Memorial, Methodist and St. Joseph's Hospitals and others from Mississippi and Arkansas. NCI Director Frank Rauscher will speak at the committee's first meeting March 30. . . . **ARTHUR HOLLEB**, ACS chief medical officer, has urged physicians to refer cases of acute lymphocytic leukemia and osteogenic sarcoma to "qualified medical and pediatric oncologists." In an editorial in the March-April issue of *Ca—A Cancer Journal for Clinicians*, Holleb says, "Our experience with cancer in childhood has not been a long and glorious record of achievement. However in recent years we have begun to see considerable promise. ALL, in the hands of experts, is now accounting for 50% five-year survival. . . It behooves every physician in this country to make sure that qualified medical and pediatric oncologists become the appropriate source of referral for children with this uncommon, potentially fatal disease. Osteogenic sarcoma seems to be yielding to this same kind of expert care."

GAO SAYS FOCAL POINT ROLE OF COMP CENTERS NEEDS TO BE CLARIFIED

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onstration programs, including establishing criteria for determining when the centers can act effectively as focal points.

The GAO report was much less critical than some NCI staff members felt it might be. One NCI executive commented, "It was rather bland." And the problems the report discusses are those NCI has been wrestling with all along.

The report will have its effect on Congress, however. Those legislators whose states or districts do not lie within the service area (120-mile radius) of a comprehensive center can be expected to use it to put new pressures on NCI, and on institutions within their districts to strive for comprehensive status.

GAO noted that NCI has said it will take about 31 comprehensive centers to serve about 180 million people. "So far, the 17 comprehensive centers have been part of institutions where excellent cancer research programs already exist and a balanced geographic distribution has not been achieved," the report said. "If NCI continues to designate centers at the top research institutions, and indications are that it will, large portions of the country will not have immediate access to comprehensive centers."

GAO criticized NCI for not giving centers any specific responsibilities to act as focal points for cancer-related demonstration activities in their areas, as Congress decreed in the National Cancer Act section authorizing the comprehensive centers. Neither has NCI evaluated the areas the centers are serving to see if they are reaching as many people as possible or if they are duplicating efforts of other centers, the report said.

"Because many centers are in cities where several institutions are sponsoring cancer research, the competition among these institutions, including the center, for federal research funds raises questions about the practicality of a focal point," GAO said. "The centers' role could be more effective if NCI would define the centers' responsibilities and the geographic areas they are to serve."

GAO was interested in another problem with which NCI has had to contend—the multi-institution centers.

"NCI expected these multi-institution centers to develop a single administrative structure, thereby enabling them to serve as a single comprehensive center and a single focal point for demonstration projects in their areas," GAO said. "During our review, however, the centers in Philadelphia and Washington had not developed single administrative structures . . . A formal cooperative effort for multi-institution centers is essential . . . We believe that NCI should stress this point in reviewing future centers and should make special efforts to see that existing multi-institution centers develop into single focal points and single comprehensive centers."

RADIATION TOXICOLOGY, HYPERTHERMIA, RADIOSENSITIZER PROJECTS APPROVED

A series of high-priority research projects, "whose impact will be felt in almost all phases of radiation therapy," has been approved by NCI's Div. of Cancer Treatment Board of Scientific Counselors. The recommendations were drawn up by a subcommittee of the board headed by Philip Rubin, chairman of the Div. of Radiation Oncology at the Univ. of Rochester.

The proposed research included basic research and clinical investigation projects in radiation toxicology, suggested by John Yuhas and Morton Kligerman; recommendations for a research program in hyperthermia, alone or in combination with radiation or chemotherapy, outlined by Max Boone, Morton Elkind, George Hahn and Thomas Ceates; and research with hypoxic cell sensitizers (radiosensitizers), suggested by Theodore Phillips and Donald Chapman.

The recommendations follow:

RADIATION TOXICOLOGY

I. Basic Research

Two major goals are proposed for this program—development of normal tissue and tumor radiation injury systems which parallel the clinical problem; and investigation of time/dose, chemical and physical means of minimizing normal tissue injury in the course of effective tumor treatment.

A. System Development

1. Normal tissues—Presently available in vivo assays for normal tissue injury are concerned with the precise quantitation of radiation responses which seldom prove to be limiting in the clinic, e.g., skin, bone marrow, (with exceptions) and gastrointestinal epithelium. Since the responses of organized tissues vary widely, it is difficult to employ these resultant data to predict the acute responses of such organs as the kidney, much less their sub-acute and late responses.

Preliminary efforts have been made to develop lethality assays based on the localized exposure of those tissues which are limiting in the clinic. While useful as a first approximation, these suffer from the uncertainties of lethal assays per se and from the fact that lethal responses may not bear the same relation to time, dose and physical factors, as do more subtle responses. It is proposed that at least the following normal tissues be the subject of intense investigation, with the goal being to develop quantitative assays of normal tissue radiation injury.

TISSUE	ASSAY
1. kidney	F, M, C
2. lung	F, M. C ?
3. salivary glands	F, M
4. colon other than epithelium	M, C
5. heart	F, M, C
6. spinal cord	F, M
7. brain	F, M

Due to the lack of detectable clonogenic potential

in any of these tissue, the techniques involved would include assays of functional impairment (F), morphologic disturbance (M), or compensatory reactions (C). Preliminary data on the first five named tissues from a number of laboratories indicate that accurate dose response curves can be obtained.

This project should receive top priority since it is a requisite for developing realistic estimates of the risks associated with present and anticipated treatment regimens. It should require the efforts of approximately 4 groups for 2 years at a cost of $75,000/year/group. The exploitation of the 2 years progress in terms of analyzing present and anticipated treatment modes will follow and require varying amounts of time depending on the particular regimen.

2. Tumor battery development—Since a wide variety of tumor types are encountered clinically it would appear unwise to champion one or another experimental tumor as being reflective of the entire problem. It is proposed that a battery of solid tumors be developed which would include both slowly and rapidly growing sarcomas and carcinomas of the mouse, all of which would be relatively weakly immunogenic. Supplementary tumors would include those which vary in immunogenicity, as well as those with a marked propensity to metastasize.

Once formed and analyzed (tumor characteristics versus radiation response), this tumor battery would proyide not only a realistic estimate of the spectrum of tumor responses to localized radiation treatment, but would also allow study of anticipated further goals, e.g., combined treatment (radiation and immunotherapy) and metastatic spread in treated hosts.

Since most of the potentially useful approaches to local tumor control hope to exploit the physiologic state of the tumor, this effect deserves high priority. It would be desirable to possess a common host for these tumors, and it is proposed that such a study be conducted by a single group with adequate access to large scale carcinogenesis experiments or by a single group with the interest in searching out the tumors which are or become available in a commonly used mouse. In either case, the effort could require up to three years, with a maximum yearly cost of $50,000. The maintenance and use of this battery would determine subsequent costs.

B. Minimization of Normal Tissue Injury

In anticipation of the likelihood that normal tissue tolerance will not exceed the radiation doses required for effective tumor control, it is proposed that three general approaches to minimization of normal tissue injury during tumoricidal treatment courses be studied: physical methods, time/dose alterations, and chemical methods.

1. Physical methods—The two major physical approaches are either covered by other funding sources at present (qualitative differences in beam characteristics) or discussed by others (hyperthermia).

2. Time/dose alterations—The conventional patterns of 5 fractions per week has evolved as a standard protocol for the mutual convenience of the patient and physician. Considering what is known of variability in both tumor and normal cell cycles and of tumor reorganization during treatment, it is unlikely that 5 equal daily doses is optimal for inhibiting all tumors and sparing all normal tissues. It is proposed therefore that certain non-conventional fractionation schemes be tested in pilot experiments to determine whether advantages can be gained by deviating from conventional methodologies. A prototype simplified comparison (rapid and slowly growing tumors versus skin) would involve the following experiments:

a) the same weekly dose given as 2, 3, or 5 equal fractions.

b) the same weekly dose given as a descending series of 5 fractions, ascending series of 5 fractions, or as 5 equal fractions.

c) comparison of greater than 1 fraction/day with conventional daily patterns.

d) week-on, week-off periods as opposed to repeated weekly treatments, especially for the treatment of slowly growing fibrosarcomas.

Those non-conventional patterns which appear to offer an advantage will be presented further.

A second area under this project would involve determination of residual injury to selected normal tissues. While clinical experience suggests that a given normal tissue cannot again be taken to tolerance levels if the tumor recurs, the data are scanty and not precise. Normal tissues which already have available assays (kidney, cord, and colon) should be exposed to near tolerance levels, and 6 months later should again be exposed to determine the extent of residual injury. Depending on the outcome of these experiments, the time course and tissue dependence of residual injury should be determined.

The entire time/dose project should require 3 years at a cost of $75,000/year for each of two laboratories.

3. Chemical interference with normal tissue injury —The general topic of radiosensitizers is covered elsewhere and the present section covers the joint use of radioprotectants and radiosensitizers. While seeming to add another variable to an already complex problem, joint drug use offers the possibility of obtaining relatively large therapeutic gains without requiring toxic levels of either drug. Two drugs, Ro-07-0582 and WR-2721 have been shown to sensitize the hypoxic fraction of tumors and protect normal tissues, respectively. Preliminary studies on the joint use of these two agents has demonstrated that their toxic mechanisms are independent and that both tumor sensitization and normal tissue protection are expressed in animals given low doses of both drugs. Since this approach offers the possibility of avoiding the toxicity which inhibits the promise of either drug alone, it should receive high priority. Due to the existence of many candidate drugs of both types and

the need to investigate more than a single tumor system, it is proposed that at least three laboratories be funded for 2-3 years at a yearly cost of $75,000 each.

RADIATION TOXICOLOGY

II. Clinical Investigations

The majority of the projects listed in Section I are not readily translatable into clinical protocols at present, but should be so within the next 2-5 years. There are a number of clinical studies which can, and should, be performed in order to exploit the anticipated gains which the basic research might provide. Likewise, a large study, designed to assess the effect of present day treatment protocols on normal tissues is provided.

A. Description of Human Tumor Kinetics and Responses

While identical experimental approaches cannot be used in the patient host, it is proposed that the same data be obtained for human tumors growing as primary explants in immunologically deprived mice. The recent development of the LASAT mouse should allow a variety of human tumors to be grown in vivo, without the complication of T-lymphocytes or B-lymphocytes mediated immunologic attack. Both normal growth patterns and radiation responses can therefore be studied. The ultimate goal is to be able to predict optimal treatment patterns for human tumors by comparing their individual growth patterns, etc. with those of the tumor battery, whose optimal treatment patterns will be known. It is proposed that at least two institutions with adequate laboratory facilities be funded for three years at $100,000.

B. Assessment of Normal Tissue Injury

Normal tissues are often, of necessity, included in the treatment volume, and receive, in most instances, doses which are less than their tolerance. By definition, tolerance is the maximum dose which can be delivered without encountering the respective clinically detectable adverse normal tissue reaction. The responses of these normal tissues which do not result in overt clinical signs go undetected and represent the bulk of our experience.

It is proposed therefore that a clinical follow-up program be instituted which 1) develops for each patient included in the study, the individualized dose estimates to each normal organ, and 2) monitors these patients such that subsequent biopsy and/or autopsy material can be obtained. The objective of these studies would be to obtain dose-response curves for normal tissue injury in patients using the techniques developed in animal systems. For each participating institution it would require a medical physicist, a technical/protocol nurse, and a pathologist, in addition to the radiotherapist. It is recommended that each participating institution (6-8 total) be awarded $100,000 per year for each of the five years of study.

HYPERTHERMIA

There has been a recent revival of interest in hyperthermia as a treatment for malignant disease based both on well documented clinical evidence of tumor regressions and on encouraging evidence from the laboratory. There is reason to believe that heat alone or in combination with radiation or chemotherapeutic drugs may greatly enhance tumor control by improving therapeutic ratios and overcoming the radioresistance of hypoxic tissues or drug resistance of various tumor cells. Before hyperthermia can be used clinically as an adjuvant to radiation or drug therapy, substantial data must be available concerning (a) normal tissue response to hyperthermia plus these two agents; (b) how heat modulates radiation or chemotherapeutic response; (c) the production and control of localized hyperthermia and resulting thermal distributions in vivo; and (d) the pathophysiology and upper limit of tolerance of systemic hyperthermia.

PRIORITIES

1. Normal Tissue Tolerances to Hyperthermia Alone or With Radiation—Just as normal tissue tolerance is the dose limiting factor when radiation is used alone, the tolerance of normal tissues will also limit the use of local or regional hyperthermia with or without radiation. Both acute and chronic quantitative end-points for a number of tissue systems should be investigated in animal systems, paying particular attention to those tissues which are most often dose-limiting in radiation oncology, i.e. spinal cord, kidney, lung, colon, liver, skin, heart, and microcirculation.

2. Quantitative Pathophysiologic Studies of Systemic Hyperthermia in Man and Animals—A major effort should be made towards assessing the extent to which systemic hyperthermia can be employed in man, since this approach is essential if hyperthermia is to be employed in the treatment of metastatic disease. This may in fact be an important application of hyperthermia, especially if combined with appropriate chemotherapeutic regimes. Hyperthermia (42° C) has been shown to be quite effective in tumor control in experimental systems when combined with anticancer drugs. Quantitative pathophysiological studies for system heat treatments up to 42° C have not been conducted in man and animals, and consequently, the effects of such levels of hyperthermia are not clearly defined.

3. The Timing of Radiation and Heating on the Relative Damage of Tumor and Normal Tissues—Because of the marked and dramatic change in thermal sensitivity when a second thermal dose follows within 12-24 hours, and the evidence that hyperthermia sensitizes cells to effects of local irradiation, a detailed investigation is needed of the role of time between irradiation and hyperthermia and the sequencing of the two modes of treatment, and of fractionation effect for hyperthermia alone or combined with irradiation on tumors and normal tissues.

4. Studies of Therapeutic Ratio for Effects in Transplantable Tumors Relative to Those in Normal Tissues—Assays of the response to hyperthermia and radiation of transplantable tumor systems and normal tissues in the same animal are necessary in order to arrive at estimates of the therapeutic ratio for a variety of treatment regimes.

5. The Effect of Hyperthermia on the Radiation Sensitivity of Anoxic and Well Oxygenated Cells—Data are appearing which suggest that the differential in radiation sensitivity between anoxic and oxygenated cells may be reduced by hyperthermic treatment. This tissue should be thoroughly explored and clarified.

6. Temperature Measurement—One of the problems which must be solved is the measurement and monitoring of thermal fields used for patient treatments. Suitable invasive techniques seem to exist or be on the immediate horizon for these measurement. Thermistor and thermocouple thermometry has developed significantly in the past few years, but these techniques are not applicable for temperature measurement in high-frequency electromagnetic fields. However, it seems desirable to stimulate development of non-invasive temperature-measuring techniques suitable for patient use. For example, the absorption of ultrasound is temperature-dependent and this may possibly supply a basis for a non-invasive technique.

7. Modalities for Production of Hyperthermia—Tentative or short-term objectives for thermal fields might be: controlled temperatures ranging from 41 to 44° C with uniformity within the thermal fields. At the present time the following methods of heating have been proposed and explored to a limited degree) regional perfusion with heated fluids, microwave heating, low radiofrequency (Rf) current fields, conventional diathermy in the Rf range, ultrasound, fluid immersion, inhalation of heated gas and thermal insulation to reduce heat loss, and whole-body heating via infra-red.

Each of these techniques has limitations and it is doubtful that any one mode will be universally applicable. Regional perfusion of extremities has been used clinically and appears to be technically feasible almost immediately. Whole-body heating via inhalation of heated gases has been used clinically but appears to be too demanding to achieve anything but limited acceptance. Immersion in fluids appears to have limited application—restricted to surface lesions—but may be useful in selected sites, i.e., urinary bladder. Infra-red heating under closely controlled conditions may be useful for whole-body hyperthermia. Depth of penetration of microwaves is frequency-dependent, with increased penetration at lower frequencies. Heating to a depth of a few centimeters seems feasible, but the technique suffers from differential absorption in tissues (greater in fat than muscle). Ultrasound provides for adequate tissue penetration, but is complicated by increased absorption in bone and at interfaces. However, there is the advantage that it can be focused much as with visible light. Heating of localized volumes of tissue by low-frequency Rf (500-1000 K Hz) current fields has been used successfully to treat spontaneous tumors in dogs and cats, both by hyperthermia alone and hyperthermia combined with radiation. Good tumor regressions have been obtained with preservation of normal tissues. The latter technique would be applied to accessible human tumors in which suitable electrodes can be implanted, or in which external electrodes or combination of implanted and surface electrodes may be used.

Support of research and development projects applied to ways and means of producing thermal fields will be necessary as a stimulus to achieve the goal of producing controlled thermal fields in man. With sufficient expenditure of effort, it seems possible to develop heating systems adequate to produce both local and systemic hyperthermia within approximately 5 years.

8. Trials on Spontaneous Tumors in Animals—These trials in animals with spontaneously arising tumors of various tumor types are exceedingly important. These studies will determine the efficacy of hyperthermia alone or combined with radiation or chemotherapeutic drugs on a wide variety of tumors of various histologies and will provide valuable experience for subsequent clinical trials in humans.

9. Preclinical Studies of Efficacy, Toxicities, Pharmacokinetics, and Cell-Cycle Effects for Hyperthermia Plus Anticancer Drugs—It will be necessary to examine the efficacy of combining a number of standard anticancer drugs with whole-body or localized tumor hyperthermia. Dosing schedules and sequencing of both drugs and heat will be studied. Toxicities of combination therapy to bone marrow will be examined in the spleen colony assay system and to the gastrointestinal tract by histological evaluation of intestinal crypts. Concomittant pharmacokinetic and tumor kinetic studies will be carried out to evaluate the effects of hyperthermia (whole-body and localized tumor) on anticancer drug distribution and cell-cycle blockade in both normal and tumor tissues.

10. Clinical Studies of Hyperthermia Plus Anticancer Drugs—It will be necessary to examine the efficacy of combining a number of standard anticancer drugs, singly or in combination, with whole-body or localized tumor hyperthermia. Dosing schedules and sequencing of both drugs and heat will be studied. Toxicity studies with respect to bone marrow will be examined in vitro and in vivo. Concomittant pharmacokinetic and tumor kinetic studies will be carried out to evaluate the effects of hyperthermia (both whole-body and localized tumor) on anticancer drug distribution and cell-cycle blockade in both normal and tumor tissues.

11. Phase I and II Clinical Trials of Radiation Plus Hyperthermia—Phase I and II clinical trials of radiation plus hyperthermia will probably focus on

two groups of patients, (a) those with apparently local disease which is poorly controlled by present treatment approaches, and (b) those with disseminated disease which is quite radiation sensitive or which responds very poorly to drug combinations and in which evidence from the laboratory suggests marked response from radiation plus hyperthermia. Until good methods of local heating and excellent thermal dosimetry can be developed, local radiation may need to be combined with systemic hyperthermia in order to investigate deep-lying tumors. Superficial or accessible tumors can be locally heated with radiofrequency current fields, especially in head and neck neoplasms where the interstitial radiation sources (e.g. radium needles) can be used as the electrodes. However, even here improved thermal dosimetry must be available before clinical trials can be initiated.

Whole-body hyperthermia plus whole-body radiation can be investigated on locally radiosensitive tumors such as myeloma, oat cell carcinoma, or perhaps non-Hodgkin's lymphoma especially of nodular histologies.

Even levels of hyperthermia which have been safely achieved systemically in man (41-42° C) can be shown in the laboratory to essentially abolish sublethal damage repair and to enhance lethal damage by a true synergism. Abolishing sublethal damage repair should be especially significant in cases in which the tumor cells show a broad shoulder in their radiation cell survival response (e.g. sarcomas) and the relevant dose limiting normal tissue has a narrow shoulder. Combining local hyperthermia with low dose rate, interstitial radiation has great appeal for early clinical investigation because (1) the tumor and normal tissue responses can be easily observed and measured, (2) it is convenient to use the interstitial sources (radium needles, iridium wires) as heating electrodes making use of an already developed heating modality, Rf current fields, and (3) evidence from the laboratory indicates greater potentiation of radiation effects by hyperthermia with lower dose rates of irradiation, as with the lower dose rate interstitial approach vs. higher dose rate external radiation.

HYPOXIC CELL SENSITIZERS

Hypoxic cells are known to be more resistant to the effects of ionizing radiation than aerated cells. Chronically hypoxic cells are known to be present in solid tumors in man and other animals. Whether or not the radioresistance of such cells is a limiting factor in the local control of solid tumors treated with fractionated radiotherapy is a subject of current debate. It appears likely that hypoxic cells are a cause of radioresistance in at least some tumors. If such cells could be selectively sensitized or the oxygen effect minimized, radiation therapy might result in considerably higher proportions of local control. High L.E.T. radiations provide lower oxygen effects are are, thus, one approach to this problem. Alternatively, the combination of chemical radiosensitizers which are selective for hypoxic cells using low L.E.T. irradiation has the potential of reducing the oxygen enhancement ratio of tumor cells as low as or lower than that observed with high L.E.T. irradiation.

Several recent reviews indicate that a number of compounds are active in selectively sensitizing hypoxic mammalian cells. Of the drugs tested to date, those of the nitroimidazole class appear to have the greatest potential because of their superior pharmacologic properties and greater effectiveness in mammalian cells. Among these compounds, Metronidazole and a compound produced by Roche, Ro 07-0582, have proven to be some of the most active in sensitizing hypoxic mammalian cells. The 2-nitroimidazole compounds (Ro 07-0582) proved to be more effective in sensitizing hypoxic cells than the 5-nitroimidazole compounds (Metronidazole). In animal systems, these compounds have proven to create x-ray dose enhancement, ranging from 1.2 to 2.4 in hypoxic cells, thus approaching the maximum oxygen enhancement ratio.

IMPORTANT BASIC SCIENCE EXPERIMENTS

Required basic science experiments can be divided into those necessary to identify new active compounds and their efficacy/toxicity ratios and efforts to further understand the potential for these compounds in tumor therapy.

In the search for a clinically useful hypoxic cell sensitizer or more useful sensitizers, the following criteria should be used as guidelines:

1. The therapeutic dose must be less than that which would give rise to toxic side effects.
2. The sensitizers should be widely distributed throughout the body.
3. The sensitizer must be capable of diffusing a considerable distance throughout a non-vascularized cell mass (tumor) to reach the hypoxic cells, which may be up to 200 microns from the nearest tumor capillary.
4. Because diffusion times may be long, it is essential that the sensitizer not undergo metabolism in the tissue. It must not be rapidly excreted.
5. The sensitizer should be effective throughout the cell cycle, since it is likely that hypoxic cells will be arrested at the G_1-S interphase.
6. Sensitization should be effective at relatively low radiation doses.

Laboratory or basic investigations of hypoxic cell radiosensitizers should concentrate on the following major areas:

a. Studies of the toxicology and pharmacology of existing compounds recognized to cause significant sensitization of hypoxic cells in mammalian tissues and tumors in vivo should be expanded to cover the necessary large animal toxicity studies required to obtain IND permission for human investigation.

b. The synthesis of new compounds with potential activity as hypoxic cell sensitizers should be stimulated.

c. Newly available compounds should be tested for

their ability to sensitize hypoxic cells in vitro, their lack of direct cell toxicity to aerated cells, their ability to sensitize hypoxic skin in vivo, and their ability to sensitize a wide range of mouse tumors.

d. Any possible action of hypoxic cell sensitizers in perturbing cell kinetics or in killing hypoxic cells should be investigated.

e. The possible interaction of hypoxic cell sensitizers with high L.E.T. radiation should be investigated.

f. Methodology should be developed for monitoring drug localization with respect to site, time, and concentration.

Hypoxic cell sensitizers should be used to study the biology of hypoxic cells and mechanisms of reoxygenation during fractionated or low dose rate irradiation.

IMPORTANT CLINICAL INVESTIGATIONS

1. Steps should be taken immediately to procure sufficient quantities of promising agents, such as Ro 07-0582 and Metronidazole, to support human clinical trials.

2. Pharmacologic studies and formulation studies allowing preparations for oral and intravenous use should be carried out with sufficient data generated to allow application for IND permission from the FDA.

3. Clinical evaluations should start in phase I and phase II trials, evaluating the toxicity of the compounds and the maximum tolerated doses, particularly doses yielding at least 200 mgm/ml of blood. Such studies should include not only blood level measurements subsequent to drug administration, but measurements of drug level in the CSF and in accessible tumors that can be biopsided.

4. Clinical studies evaluating the effect of the compounds alone on tumor, the effect of the compounds prior to irradiation, and the effect of the compounds subsequent to irradiation should be started.

5. Phase II clinical trials attempting to identify those tumors in which apparent enhanced response occurs should be initiated as soon as phase I trials are completed.

6. Phase III trials with randomization between conventional radiotherapy alone and optimum radiotherapy plus sensitizer (probably 2 or 3 fractions) should be begun in those sites where response was apparently enhanced in the phase II trials.

7. Methods for better identification of drug concentrations as a function of tissue, tumor, and time should be developed for human use.

8. Simple methods for administration of large drug volumes should be developed and methods for minimizing side effects developed and applied.

TIME TABLE AND PRIORITIES

Clinical Studies—There are sufficient promising radiosensitizers available to begin the onset of clinical trials in the near future. The following time table is suggested:

1. Initiate studies with Metronidazole using metastatic disease with preferably multiple sites of metastases to evaluate drug response alone and drugless radiation response. Time frame: 6 months.

2. Perform large animal toxicology studies with doses of Ro 07-0582, equivalent to at least 10 gm dosages in the human, using both oral and intravenous routes.

3. Begin necessary steps to obtain at least 40 kg of Metronidazole and 40 kg of Ro 07-0582 within the next 6 months.

4. Begin clinical phase I-II trial of Ro 07-0582. Time frame: 1 year.

5. Follow phase I studies of Metronidazole and Ro 07-0582 with phase I studies of additional compounds as identified through screening and toxicology testing. Time frame: 2 years.

6. Support increased laboratory screening of new compounds for sensitizing activity and toxicity in rodent systems following preliminary screening in cell culture systems.

7. Stimulate synthesis of new compounds through contracts or grants to corporations having expertise in this area. Time frame: 3 years.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS SCHEDULED IN APRIL, MAY

Committee on Cancer Immunotherapy—April 1-2, Landow Bldg Room C418, open April 1 8:30-9 a.m. (Previously scheduled to start March 31).

Recombinant DNA Molecule Program Advisory Committee—April 1-2, NIH Bldg 31 Room 8, open April 1 9 a.m.–5 p.m., April 2, 11 a.m.–adjournment.

President's Cancer Panel—April 1, NIH Bldg 31 Room 7, open 9:30 a.m. noon.

Committee on Cancer Immunobiology—April 5, NIH Bldg 10 Room 4B14, open 2–2:30 p.m.

Third Symposium of CMEA Countries on Toxicological Testing of New Drugs—April 6-8, Prague.

Committee on Cancer Immunodiagnosis—April 6, NIH Bldg 10 Room 4B14, open 1–1:30 p.m.

Cancer Institutional Fellowship Review Committee—April 7-10, Queen Mary Hyatt Hotel, Long Beach, Calif., open each day 8:30–9 a.m.

Virus Cancer Program Scientific Review Committee B—April 7, Frederick Cancer Research Center, open 9–9:30 a.m.

Oncology Nursing—Major Treatment Modalities Seminar—April 8, Roswell Park, registration required.

Committee on Cytology Automation—April 8-9, NIH Bldg 31 Room 4, open April 8, 9–10 a.m.

National Prostatic Cancer Project Working Cadre—April 11-12, Sheraton Harbor Island Hotel, San Diego, open April 11, 10–10:30 a.m.

National Pancreatic Cancer Project Working Cadre—April 12-13, Sheraton Hotel, New York City, open April 12, 7–7:30 p.m.

First International Symposium on Facial Prosthetics—April 19-23, Arnhem, Netherlands.

Biometry & Epidemiology Contract Review Committee—April 20-21, Landow Bldg Room C418, open April 20, 7–11 p.m.

First International Congress on Patient Counseling—April 21-23, Amsterdam, Netherlands.

Combined Modality Committee—April 21, NIH Bldg 31 Room 8, open 8:30–9 a.m.

Clinical Trials Committee—April 22, NIH Bldg 31 Room 4, open 8:30–9 a.m.

Committee on Cancer Immunotherapy—April 22, NIH Bldg 10 Room 4B14, open 1–1:30 p.m.

Carcinogenesis Program Scientific Review Committee A—April 22-23, NIH Bldg 37 Room 1B04, open April 22, 9–9:30 a.m.

Carcinogenesis Program Scientific Review Committee B—April 22-23, NIH Bldg 31 Room 5, open April 22, 9–9:30 a.m.

Cancer Control Intervention Programs Review Committee—April 23, NIH Bldg 31 Room 4, open 9–9:30 a.m.

Drug Development Committee—April 26, NIH Bldg 31 Room 7, open 10 a.m.–adjournment.

Third International Symposium on Detection & Prevention of Cancer—April 26-May 1, New York City.

Virus Cancer Program Scientific Review Committee B—April 26-27, Landow Bldg Room C418, open April 26 9–9:30 a.m.

International Symposium on Medical Genetics—April 27-29, Debrecen, Hungary.

Developmental Therapeutics Committee—April 28-29, NIH Bldg 37 Room 6B23, open April 28, 8:30–9:15 a.m.

Board of Scientific Counselors of the Div. of Biology & Diagnosis—April 30-May 1, NIH Bldg 37 Room 4E08, open April 30 9 a.m.–5 p.m.

Twelfth Annual Meeting of the American Society of Clinical Oncologists—May 4-5, Toronto.

Sixty-seventh Annual Meeting of the American Assn. for Cancer Research—May 6-8, Toronto.

Eleventh Canadian Cancer Research Conference—May 6-8, Toronto.

Postgraduate Course on Immunovirology of Cancer—May 10-22, Lyon, France

Cancer—Towards A Solution—May 11, Marie Curie Memorial Foundation, London.

First Meeting of the European Nuclear Medicine Society—May 12-15, Lausanne, Switzerland.

Seminar on Malignant Lymphomas—Recent Trends in Classification and Therapy—May 13, Roswell Park, registration required.

Eleventh Tutorial on Clinical Cytology—May 16-22, Chicago.

Yale Neuro-Oncology Course—Biology, Epidemiology, Diagnosis and Treatment of Brain Tumors—May 17, New Haven.

National Conference on Radiation Oncology—May 27-29, San Francisco.

SOLE SOURCE NEGOTIATIONS

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

Title: Procurement of leadless internal temperature measurement study
Contractor: RCA Research Laboratories.

CONTRACT AWARDS

Title: An organized approach by the family physician to the diagnosis and management of selected forms of cancer
Contractor: American Academy of Family Physicians, Kansas City, Mo., $86,868.

Title: Supply of special primate RNA tumor viruses and virus infected cells
Contractor: HEM Research Inc., Bethesda, Md., $355,926.

Title: Breast cancer detection demonstration project
Contractor: St. Vincent's Medical Center, Jacksonville, Fla., $252,500.

Title: Propagation and Seroepidemiology of EB viruses
Contractor: Children's Hospital of Philadelphia, $589,679.

Title: Electron microscope studies of tumor virus nucleic acids
Contractor: California Institute of Technology, $324,855.

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 76-S-12

Title: *Long term carcinogenesis bioassays using rodents*
Deadline: *June*

Studies will include dosages via gavage, skin-painting, dosed-water, dosed-feed, and intraperitoneal.

This solicits proposals toward a subcontract in the research area indicated. Offerors should have experience in carcinogenesis bioassay studies and testing. A board-certified veterinary or medical pathologist with experience in laboratory animal pathology, an HT/ASCP registered technician, a chemist, and a toxicologist must be available for the program. Facilities for dosing and maintaining approximately 6,000 animals in isolated and stringently controlled, clean conditions are necessary.

Pre-proposal conference is to be held on April 26 at 9 a.m. at Tracor, Inc., 1601 Research Blvd., Rockville, Md., in the main conference room. Attendance by written request only.

Contact: Subcontract Administrator
Tracor-Jitco Inc.
1776 E. Jefferson St.
Rockville, Md. 20852
301-881-2305

The Cancer Letter—*Editor* JERRY D. BOYD

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