THE CANCER LETTER

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

Vol. 5 No. 16

April 20, 1979

Subscription $125.00 per year

HISTORICAL VS. CURRENT CONTROLS: COMPARABILITY, ETHICAL ISSUES ARGUED BY MOERTEL, FREIREICH

Ethical issues involved in the conduct of clinical trials have been a source of concern and sometimes frustration for cancer treatment investigators, particularly when it comes to deciding between randomization and historical controls.

As was expected, the confrontation between the two most outspoken investigators on opposite sides of that issue provided plenty of grist for that argument recently at the Second International Con-

(Continued to page 2)

In Brief

MUGGIA LEAVING NCI FOR NYU IN SEPTEMBER; SEMINAR PLANNED ON RADIATION EXPOSURES

FRANCO MUGGIA, associate director for Cancer Therapy Evaluation in NCI's Div. of Cancer Treatment, will leave next September to become professor of medicine, director of the Div. of Oncology and associate director of the cancer center at New York Univ. DCT Director Vincent DeVita is looking for candidates to replace Muggia; those interested may write to him at NCI, Bldg 31 Rm 3A52, NIH, Bethesda, Md. 20014, or phone 301-496-4291. . . . **PHYSICIANS HAVE** been swamped with questions about radiation exposure since the nuclear reactor accident in Pennsylvania. Allegheny General Hospital in Pittsburgh and the Mideast Center for Radiological Physics are sponsoring a seminar April 25 on "Known Effects of Low Level Radiation Exposures" to help physicians and others answer some of the questions they are being asked. Speakers will include NCI Director Arthur Upton; Robert Conard, former head of the Marshall Islands fallout study; Jacob Fabrikant, National Academy of Sciences; and Victor Bond, Brookhaven National Laboratory. The seminar will be held 10 a.m.–3 p.m. at the Airport Holiday Inn in Pittsburgh. Call Peggy Flynn, 412-237-4012, to register. . . . **CORRECTION:** The proposed new funding mechanism, the cooperative agreement, which NCI is considering adopting for the Cooperative Groups, will not be "initiated by NCI" (*The Cancer Letter,* April 6). Cooperative agreement grants would be investigator initiated, as are the present R10 Cooperative Group grants. The only "initiative" by NCI would be the decision to drop the R10 in favor of the new mechanism, NCI executives say. . . . **WINNERS OF THE** $100,000 General Motors Cancer Research Prizes were Henry Kaplan, Stanford, for his role in the development of high cure rate therapy for Hodgkin's disease; Richard Doll, Oxford Univ., for leadership in studying the environmental causes of cancer; and George Klein, Karolinska Institute, for his pioneering work on the relation of cancer and the immune system. They were selected from more than 600 nominations received from 17 countries.

MOERTEL SAYS PROGRESS MAY INVALIDATE HISTORICAL CONTROLS FOR MANY TRIALS

(Continued from page 1)

ference on the Adjuvant Therapy of Cancer in Tucson.

Charles Moertel, director of the Mayo Comprehensive Cancer Center, believes that not only is randomization ethical in most cases but it is also the only way that reliable comparisons can be made in many phase 3 and 4 studies.

Emil (Jay) Freireich, chief of Developmental Therapeutics at M.D. Anderson Hospital, believes that randomization "borders on the unethical" and that historical controls can be at least as reliable as randomization, if not more so.

Moertel opened the debate in his presentation on adjuvant therapy of gastrointestinal tumors. Improvements in surgery and pathology make it difficult or impossible to use historical controls in colorectal carcinoma studies, Moertel contended.

"In C Dukes lesions, those with nodal involvement, cure rates are generally quoted in the 20-30% range," Moertel said. "It has also been assumed that the results of surgical treatment have essentially been at a plateau over the past quarter century. As we consider surgical adjuvant therapy, it is important that we scrutinize such statistics and assumptions to be sure that they really apply to large bowel cancer today.

"National end result statistics would make it appear that there has, in fact, been a steady improvement in five year survival over a 30-year period—from 53 to 71% in localized disease, and from 27 to 44% in regional disease. . . . The contention that improved surgical technique has produced these apparently improved results may be true, but this is providing surgical pathology technique has not changed over this same period of time. If, however, the pathologist has been progressively more meticulous in his staging, a lot of tumors that were called B Dukes yesterday are today going to be moved into the C Dukes column with a resultant apparent improvement in survivorship. As the quality of either surgery or surgical pathology or both improves in our university and community cancer centers, we must anticipate that stage for stage the reported results of surgical treatment are going to be better today than they were yesterday.

"All of this is background for the conclusion that if we apply some type of surgical adjuvant intervention to patients today, and compare results to those we achieved yesterday, we are going to have a positive study whether the surgical adjuvant treatment is effective or not. Just a cursory review of the literature will quickly show that historically controlled surgical adjuvant studies are always positive—this for literally any type of cancer."

Freireich had his chance to respond during a panel discussion which he chaired with Moertel.

"I heard two statements about historical controls that knocked me off my chair," Freireich said. "Knowing Dr. Moertel, I understand his bias. There were glaring deficiencies in his interpretation of historical data. Despite what Dr. Moertel said, there is no quick fix. He pointed out, in a clear moment, that randomized trials can give incorrect results. We won't do ourselves or science any good by flat out saying that historical controls always are worse (than treated patients in a study). That's not only silly, it's false."

Freireich suggested that two of "Freireich's Laws" should be invoked in developing experimental plans:

"One. You cannot replace the human frontal lobe with a checkoff sheet. There is no replacement for careful, thoughtful analysis of data. There will be and are situations where historically controlled studies are clearly superior to randomization. And there may be times when randomizing is better.

"The randomized trial, even when conducted by the best of us, including Dr. Moertel, borders on the unethical. Ed Gehan (head of the Dept. of Biomathematics at M.D. Anderson) has said that the best criteria for determining what is ethical is to find out which plan would be chosen by statisticians when they have cancer." Freireich said that he has known five statisticians who had cancer. "They asked who was the best doctor available to treat their disease. None asked which randomized trial they should select.

"We cannot allow ourselves to become so marginally ethical that the patients reject us," Freireich continued.

"Freireich's Law No. 2," he said, is that "all knowledge is historical, and for those who feel the best controls have relevance, they are the best controls."

Moertel responded by saying, "I think you and I are a lot closer on how to manage clinical trials than you may think." He referred to an article Freireich wrote for the *New England Journal of Medicine* in which he described criteria and justification for historical controls. "I found little to disagree with," Moertel said. "The problem is that, although you write this so beautifully, you don't practice it yourself."

An example for the proper use of historical controls would be when there is substantial evidence for a big difference between treated and untreated patients. "I agree. But you take this same principle and use it where it is not indicated," Moertel said. "Also, you point out that it is necessary for historical controls to be tightly aligned to the treatment group . . . but you don't practice it. . . . When you get into 5-FU, methyl CCNU, with and without BCG, you can't turn the clock back to neanderthal days. Those studies are not proper for historical controls."

Moertel said he agreed that it was "nonsense" to

suggest that phase 1 trials be randomized, as demanded (so far to no avail) by R.S.K. Young, FDA group leader for oncology.

Freireich commented, in comparing applause received by Moertel to his own from the approximately 1,000 physicians at the conference that "you have won round one. Round two is yet to come."

Emil (Tom) Frei, director of the Sidney Farber Cancer Institute, also a member of the panel, said, "No patient was ever cured by statistics. The problem with this discussion is that it revolves around statistics. It is more important to do the study right." Frei noted that many of the papers presented at the conference called for new anticancer agents. "I want to emphasize that I'm not sure we're doing right with the agents we have, particularly 5-FU. This is an active agent. One can get steep dose response rates. Most of the doses (used in trials) are relatively trivial, intervals are long, and 5-FU can be compromised by nitrosureas. In osteosarcoma, the difference between successful and unsuccessful studies probably is due to dose rates.

"The direction to go," Frei continued, "is to increase doses up front. You may have a problem with patients, but that probably can be counterbalanced by shortening the treatment period. The problem is to eradicate micrometastases early. Short term, intensive treatment is the way to go. It is likely that 5-FU will work if used properly."

Frei said he wanted to emphasize: The best surgery will be performed by skilled, experienced surgeons. "The same goes for radiotherapy. And if chemotherapy is to be done effectively, it needs to be done by someone with expertise in medical oncology."

Bernard Fisher, chairman of the National Surgical Adjuvant Breast Project and another panel member, said he disagreed with "Freireich's Law No. 1, that you can't replace the human frontal lobe with a checkoff list. In some cases I know about, it would be more desirable to have a checkoff list."

Fisher said that "as a lab investigator, I would never think of doing an experiment without a concomitant control. In clinical trials, because of the heterogeneity of humans, I wouldn't do less than with animals. A clinical trial is a scientific problem solving exercise. To compare, you have to have comparability. If you are going to use historical controls, the burden is on you to show proof of comparability."

"As it is with randomized trials," Freireich said.

"Exactly. Exactly," Fisher agreed.

John Ultmann, director of the Univ. of Chicago Cancer Research Center, presented an overview of the conference. On the issue of historical vs. randomized controls, Ultmann said that most of the conference participants seemed to agree current controls "are justified when you aren't sure that benefits outweigh the risks, especially when you want to detect small differences."

SURGICAL, RADIATION ONCOLOGY NEEDS DESCRIBED AT CLINICAL TRIALS REVIEW

"The present status of surgical oncology in the United States today can be summarized in one word: disaster," Donald Morton, UCLA surgeon, told the NCI Div. of Cancer Treatment Board of Scientific Counselors at the Board's review of clinical trials.

Morton is a former member of the Board; during his tenure, he argued successfully for an increased effort by DCT in support of surgical oncology. The result was the new grants program announced last December (***The Cancer Letter,*** Dec. 1), which DCT will fund up to $1 million a year.

Morton and a Board surgical committee chaired by Bernard Fisher also had recommended that DCT establish a Surgical Oncology Section, which DCT is now organizing. But those two actions are just a small part of the effort that is needed to bring surgical oncology into full partnership with medical and radiation oncology, Morton said. His statement (in part) follows:

During the past two decades, a concerted effort has been directed toward developing and strengthening medical and radiation in this country. Funds and programs have been made available and implemented for that purpose. Support for basic scientists interested in cancer research has flourished. Training programs at all levels (pre- and postdoctoral) have, within a few years, developed an entire generation of clinical and basic research specialists in these disciplines.

In contrast, despite the dominant role of surgery, both past and present, in the management of patients with common solid tumors, there has been almost total neglect either by omission or commission in making available the necessary resources and more importantly the intellectual commitments which would have permitted the development of surgical oncology in a fashion commensurate with that of the other disciplines. Whether this event may be ascribed to the fact that there may not have been progressive, unified surgical leadership promoting their cause as had existed with the other specialties or because it was a constricted view of those in policy making positions (representatives of other disciplines) that surgeons, surgery and surgical science could make no further contribution to the advancement of oncology is irrelevant. The fact is that this has occurred and requires correction. Due to this omission, only a handful of individuals and a miniscule number of training programs represent the leading edge of surgery in so far as oncology is concerned.

The tragic and most important consequence of this situation is that the potential contributions in clinical and basic research from more than a generation of talented young surgeons has been under-developed. The biologic and physiologic, as well as conceptual contributions which surgeons have made since the second world war and which were a major factor responsible for progress in cardiovascular, transplantation and gastrointestinal fields, for the most part, have not been realized in oncology.

In order to summarize the present status of surgery in relationship to a number of problem areas I will make a few observations on the present status of surgical oncology.

A. Paucity of surgical oncologists

It has been estimated that less than 20% of the university

medical centers have established divisions of surgical oncology. Even in those centers with established divisions, the number of faculty are barely adequate to cover the clinical workload and have little time for research. Since cancer makes up approximately 40% of all surgical practice, it is obvious that there is greater need for well trained surgical oncologists.

This paucity of surgical oncologists is immediately obvious in two very important areas:

1. Many of our comprehensive cancer centers have only token representation for surgical oncology and in very few centers does the level of surgical oncology approach that of medical oncology and radiation therapy. However, each of these centers has surgeons who are willing to operate on cancer patients but unwilling to make the intellectual commitment to study the disease. The absence of oncologists dedicated to surgery is accepted by the reviewing committees which would never accept a general radiologist as an acceptable replacement for a radiation therapist.

2. The lack of surgical oncologists has created tremendous problems in relationship to peer review for surgical oncology research grants and project proposals both in study sections and at site visits. As a result, there is all too frequently a difference in orientation by reviewers who fail to appreciate the true significance of a proposal because of their lack of familiarity with the discipline. When priorities for funding are established, those with surgical biological significance are apt to be at a disadvantage. Thus, the all too familiar "approved but not funded" classification frustrates the young surgeon attempting to embark on a career in academic surgical oncology research.

B. Training programs in surgical oncology

Despite the great paucity of surgical oncologists, there are presently only three NCI funded surgical oncology training programs which have a combined capacity to enter five or six new surgical oncologists per year. At this rate, surgical oncology will never be able to train sufficient surgeons who have cancer as their primary area of clinical interest and basic research. Thus, it is clear, the multidisciplinary approach to cancer therapy will be hampered by the lack of skilled surgical oncology input.

C. Lack of financial support for surgical oncology

Last year, the Div. of Cancer Treatment estimated that approximately $1.6 million per year was spent on surgical oncology research. With the new program, it is estimated that this figure may increase to approximately $2.6 million per year. Thus, the level of support of surgery research in the National Cancer Program is miniscule compared to support for medical oncology and radiation therapy. As a result, only a miniscule number of surgical oncology programs have funding adequate to provide research opportunities for young surgeons interested in surgical oncology.

RECOMMENDATIONS

A. The development of surgical oncology must be recognized as a national priority. When one reflects that over 50% of the patients with cancer in this country today are treated primarily with surgery, it is difficult to defend the present status of surgical oncology research and allocation of resources. Since surgery is such a frequently used modality, even a small improvement in surgical treatment will result in significant benefits to cancer patients. Therefore, this underemphasis on surgical oncology must be corrected as soon as possible.

B. We believe the development of surgical oncology would be best accomplished by a plan similar to that embarked upon by a committee headed by Dr. Henry Kaplan appointed by NCI to foster the development of radiation therapy. This program has been eminently successful in bringing radiation therapy to its present stage of development. In order to accomplish this, we would request that the Div. of Cancer Treatment sponsor a meeting of the Surgical Oncology Research Task Force to draw up a formal proposal to submit to NCI for the development of surgical oncology.

C. A portion of the NCI budget should be marked specifically for the development of surgical oncology research and and training. The correct portion of the budget which should be designated is obviously a matter for discussion. On the one hand, since over 50% of the cancer patients in the United States are treated today primarily by surgery one might feel that 50% of the $900 million NCI budget would be a fair figure. At the other extreme is the 0.3 of 1% which is now devoted to surgical oncology. Obviously, between these two extremes a reasonable compromise could be developed. Once the dollar amount had been agreed upon, these funds should then be allocated in the following ways:

(1) Surgical oncology training centers and programs.

Since only through training will it be possible to upgrade this specialty and make available the number of surgical oncologists required to enhance the contribution of that specialty it is recommended that:

(a) Funds be set aside specifically for the development of surgical oncology departments or centers in cancer centers and medical schools.

(b) NCI training awards in surgical oncology be greatly increased.

(c) Funds be made available to attract young surgeons at the completion of their residencies into academic junior faculty level positions in the specialty of surgical oncology.

(2) Research funds for surgical oncology.

Contracts or research grants should be made available specifically for research in surgical oncology.

D. NCI should establish a study section for surgical oncology to which grants and contracts would be referred for review. The format for this study section could be similar to the radiation therapy study section.

E. Each NCI clinical review group, task force, or advisory committee should have representation by surgical oncologists equal to representation by medical oncologists, radiation therapists, and basic scientists.

As summarized above, surgical oncology may be regarded as a minority group in the community on oncologic specialties. It is financially underprivileged, under-represented in decision making committees, underdeveloped, disorganized and failing to recognize its potential in cancer research, training or clinical care. I believe the program described above should begin to do for surgical oncology what similar programs have accomplished in medical and radiation oncology.

Simon Kramer, chairman of the Radiation Therapy Oncology Group, described progress in that field including radiation therapy achievements in Cooperative Group research, and listed needs of radiotherapy.

"Radiation therapy is a small but well organized oncologic discipline," Kramer said. "It treats roughly one-half of all cancer patients either alone or in combination with other disciplines. Eighty-seven percent of all radiation therapy patients are being treated by some 1,350 fulltime radiation therapists. The field is progressing rapidly and has in no way reached a plateau. In fact, there are excellent prospects for the in-

creased use of radiation therapy with the development of particle therapy, sensitizers and hyperthermia for loco-regional control with the likelihood of an excellent quality of life. There is also the probability that the number of cures will be greatly increased when systemic therapy can take care of systemic micrometastases. We project that at that stage radiation therapy could be employed in two-thirds of all cancer patients with an appreciable salvage of the 100,000 patients presently dying of local and regional failure."

Kramer's statement in part:

A master plan for radiation therapy research was developed approximately two years ago, which deals with the major areas of radiation therapy research and sets priorities in these areas. This plan has already been widely utilized by the Div. of Cancer Treatment in setting operational priorities for radiation therapy, through the mechanism of its Radiation Oncology Coordination Subcommittee.

The Radiologic Physics Center was initially developed and funded through two of the radiation therapy studies, in conjunction with the American Assn. of Physicists in Medicine. The Radiologic Physics Center now acts as a resource to all Cooperative Group studies involving radiation therapy.

The radiation therapists in the Cooperative Groups have assumed a role of leadership in the radiation oncology community by emphasizing the areas of research and by communicating their findings. The need for specific modern radiation therapy techniques and the need for detailed dosimetry requirements and radiation therapy procedures have been emphasized through workshops and publications. Their efforts have focused on radiation therapy questions in clinical trials. From the beginning, special stress has been placed on studies in potentially curable patients. In RTOG over 60% of all patients fall into that category. Radiation therapy has had long standing cooperation with the surgical disciplines and this has enabled us to develop multidisciplinary protocols in those areas where radiation therapy has a primary impact. RTOG has developed an initial registry of all patients seen by the participating members so that a base line of the total practice of the membership can be developed. In this way appropriate areas with adequate patient accession for future studies can be determined and the reasons assessed for non-accession of potentially suitable patients. Our findings have been disseminated to the radiation therapy community and we plan to validate the acceptance of our findings for routine radiation therapy practice.

Through the mechanism of the outreach program, funded by the Div. of Cancer Control & Rehabilitation, a large number of community hospitals has been involved in participation in the protocols, either in randomized studies or by accepting the best current practice control arm. This has led to considerable upgrading, not only in the practice of radiation therapy at the community hospitals by adherence to appropriate treatment planning, dosimetry and treatment techniques, but has led to an improved multidisciplinary approach to cancer patients.

As biologic advances have been made, particularly in overcoming the problem of the hypoxic cell element in tumors, these advances have been translated into appropriate clinical trials. For example, phase I studies on misonidazole have now been completed and phase II trials are in progress. The value of local hyperthermia is being established in phase I studies. The overall management of the national clinical trials in particle radiation has been undertaken by RTOG. There are currently nine phase III protocols for neutron beam therapy and over 380 patients have been entered so far. Clinical trials in pi meson therapy and in heavy stripped nuclei therapy have been initiated. In all these studies common control arms are used.

In the area of quality control, radiation therapists have been pre-eminent. Standard radiation therapy treatment planning techniques and dose/time systems have been adopted. We have developed on line quality control procedures which involve review of the treatment plans, the dosimetry and localization films within seven days of a protocol patient being entered. As each patient completes his treatment all physical parameters and total dose delivered are reviewed. These detailed quality control procedures have been found extremely useful for the evaluability and protocol adherence of patients entered into trials and verification of dose delivery. Similar quality control procedures are now being implemented for surgical and chemotherapeutic participation in RTOG.

Special needs in radiation therapy for Cooperative Group studies

1. There is a need to develop intergroup agreement on appropriate radiation therapy in studies on patients with essentially similar disease. This is being addressed by the Council of Radiation Oncology Committee chairpersons in the Cooperative Groups. At present such groups of patients are often studied by different Cooperation Groups within the same institution calling for different radiation therapy techniques and doses within the same department, thus making unified departmental policies impossible. Similar problems may exist in other disciplines.

2. We need to develop prognostic indicators that characterize both disease and patient to define relatively homogeneous patient groups in whom clinical trials can proceed. At present, groups of patients with a specific diagnosis are collectively entered into a study to compare different treatment arms. Yet the biology of their tumor may be so different that it overwhelms any effect of intervention.

3. There is need to establish a base line on denominators for normal tissue morbidity of curative radiation therapy. This could best be achieved by appropriate patient registries so that a true incidence of such morbidity can be determined. This is essential to be able to arrive at a judgment in combined modality therapy as to the causation of morbidity by combined modality.

4. We must establish a matrix of scoring systems. The Karnofsky scale is excellent in assessing the effect of palliative therapy, but in the cured patient it is necessary to establish a scoring system that allows us to distinguish between the effects of the disease and effects of treatment and to measure the quality of life.

5. A major problem is the statistical methodology for prospective trials. While randomized prospective trials clearly represent an excellent statistical method, it introduces difficulties when one is dealing with potentially curable patients. Rather than seeing the physician, in whom he has placed his trust, make the decision on how he is to be treated, the patient must be told that there may be two or more apparently equally good ways of treating him and that the decision is made by random selection. This is disturbing both to referring physician and patient and leads to a considerable loss of potential participants. A different type of randomization, as suggested by Dr. Zelen, should be explored, as should the possibility of matched pair analysis.

There are particular needs for radiation therapy support in

the Cooperative Groups as follows:

The collaborating disciplines of the mutimodality groups are rarely supported adequately at the institutional level. The radiation therapists in one institution often participate in the work of multiple Cooperative Groups. In the aggregate this represents a considerable effort, yet it is poorly funded, if at all. Similarly, there is inadequate support for surgeons, medical oncologists and pathologists at the institutional level in RTOG. Although the major emphasis of this group is toward radiation therapy, modern studies can hardly be undertaken without the collaboration of these disciplines.

Support is needed for the further development of particle therapy. Neutron beam clinical trials are in progress, but are severely handicapped by inadequate equipment. A number of clinically optimized hospital based machines are needed to conclude these studies in a reasonable time frame. Continued support is also needed for trirals with pi mesons, heavy stripped nuclei and protons.

Research in radiation sensitizers and protectors must be expanded. Better electron affinic and other sensitizers must be developed and toxicology testing done before clinical trials can be initiated. Local hyperthermia holds great promise. There is a pressing need to develop equipment for deep local heating and for thermometry.

Perhaps our greatest need lies in the precise delineation in deep seated tumors. Modern diagnostic technology such as CT scanning, positron emitting computerized tomography and ultrasonography are advancing our capabilities enormously. Their applications to tumor definition, radiation therapy planning and measurements of local control must be evaluated.

NCI CONTRACT AWARDS

Title: Carcinogenesis in vitro: Initiation and promotion, continuation
Contractor: Univ. of Southern California, $319,293.

Title: Breast Cancer Detection Demonstration Project, renewal
Contractor: Georgetown Univ., $328,876.

Title: Activities in support oflprimary drug screening program
Contractor: IIT Research Institute, Chicago, $898,340.

Title: Operation of an animal viral diagnostic laboratory, five month extension
Contractor: Microbiological Associates, $97,500.

Title: Organ culture assay of vitamin A analogs, continuation
Contractor: Southern Research Institute, Birmingham, $110,000.

Title: Facility for supplying immune related cell lines
Contractor: Salk Institute, $77,497.

Title: Data research analyses for Breast Cancer Treatment Program, continuation
Contractor: EG&G/Mason Research Institute, $98,257.

Title: Development of a tissue culture transformation system
Contractor: Columbia Univ., $105,919.

Title: Detroit Population Based Cancer Registry, continuation
Contractor: Michigan Cancer Foundation, $668,796.

Title: San Francisco Bay Area Resource for Cancer Epidemiology, continuation
Contractor: California State Dept. of Public Health, $90,000.

Title: Comprehensive field and laboratory research program on etiology and epidemiology of human cancer, continuation
Contractor: Univ. of Southern California, $65,000.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the contract officer or specialist named, NCI Research Contracts Branch, the appropriate section, as follows:
Biology & Diagnosis Section and Viral Oncology & Field Studies Section—Landow Building, Bethesda, Md. 20014; Control & Rehabilitation Section, Carcinogenesis Section, Treatment Section, Office of the Director Section—Blair Building, Silver Spring, Md. 20910.
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP N01-CP-95621

Title: *Data and information resources*
Deadline: *June 20*

The Carcinogenesis Testing Program of NCI is interested in obtaining proposals to develop resources for data and information activities. The activities include identification of relevant material, then gathering, collating, storing and analyzing this data/information so that the requestor has reports or products which are accurate, timely and complete.

In addition, this RFP contains a component for the evaluation of microcomputer/minicomputer hardware designs and operating systems.

Contract Specialist: Ursula Evans
Carcinogenesis
301-427-7914

RFP NCI-CM-97257

Title: *In vitro and in vivo screening of radiosensitizers*
Deadline: *Approximately June 1*

The Developmental Therapeutics Program of NCI is seeking organizations having the necessary experience, scientific and technical personnel, and physical facilities to perform in vitro and in vivo screening of radiosensitizers.

Tasks will be (a) collection of physical-chemical data, such as electron-affinity by pulse radiolysis, half-wave potentials, or related techniques; lipid/-water partition coefficients; and aqueous solubilities

on approximately 500 compounds per year; (b) in vitro evaluation of cytotoxicity and sensitization of hypoxic mammalian cells to radiation on about 100 compounds per year; (c) in vivo evaluation of the radiosensitizing potential of about 30 compounds per year using three different tumor systems from the DCT panel of radiosensitizer mouse tumor screens (C3H mammary carcinoma, Lewis lung carcinoma, B16 melanoma and EMT6 tumor; and (d) the maintenance of a conventional mouse colon capable of supporting 1,000 mice per week.

Each tumor system will be measured by a different endpoint (regrowth delay, tumor cell survival, and modification of the radiation dose required to cure 50% of the tumors) for a total of three endpoint evaluations, as described in the Div. of Cancer Treatment Linear Array for Radiosensitizers (February 1978 edition), which is available on request.

The in vivo evaluation is considered to be the most important task to be performed on this contract. Due to the specialized nature of some of the equipment, such as the pulse radiolysis equipment, the collection of physical-chemical data may be performed on a subcontract. Compounds to be tested will be supplied by the government.

Contracting Officer: John Thiessen
Cancer Treatment
301-427-8125

RFP NCI-CM-97291

Title: *Administrative and statistical support for the endometrial carcinoma contracts program*

Deadline: *June 1*

The Cancer Therapy Evaluation Program of NCI is seeking an organization having capabilities and facilities for monitoring, coordinating, preparing and maintaining materials and reports, as well as serving as the statistical center for the Endometrial Carcinoma Contracts Program.

The contractor selected shall provide administrative support and manage the organization, coordination, preparation and communication of materials generated by the Endometrial Carcinoma Contracts Program. The contractor will also be required to assist in protocol design, perform randomization of the clinical trials, and provide all statistical support necessary for conduct and analysis of the clinical trials. It is estimated that 180 patients per year will be accrued to this study.

The contractor must work closely with the project officer and have experience in the area of services for support of cancer clinical trials and experience in working with related task forces, cooperative groups, and projects involved in similar research. It is anticipated that an incrementally funded contract will be awarded for a period of three years.

Contract Specialist: Charles Lerner
Cancer Treatment
301-427-8125

RFP NCI-CM-97251

Title: *Operation and maintenance of biological data processing system*

Deadline: *Approximately June 15*

NCI will make available to interested contractors a request for proposals for data processing services. Respondent's facility must be within a 25 mile radius of NIH Bethesda, Md. facilities.

The contractor shall furnish all necessary personnel of requisite caliber, labor, materials, supplies, equipment and facilities (except as furnished by the government); shall operate and maintain the biological data processing system (the main program line system), and several sub-systems such as the natural products data processing system, plant header system, combination chemotherapy data processing system and the solid tumor system, and shall provide data processing support and services including statistical support for ongoing programs for the Developmental Therapeutics Program.

The operation and maintenance of these systems shall be accomplished so as to provide data processing functions on a fixed schedule requiring timely completion of inputs and outputs, utilize prescribed input and output forms, formats and procedures for data preparation, dissemination and control, and documented programs. Due to the dynamic nature of the systems, inputs and outputs, as well as the programs, are subject to change. There are approximately 131 computer programs in these systems.

To be considered for such a contract, candidates must show a minimum of two to three years experience with large scale biomedical data processing systems and competence to perform statistical analyses. The contractor must also demonstrate the ability to assume the responsibility of the contract without a break in the data processing cycle which is every other week.

The contractor shall submit all weekly inputs and outputs of data processing system program to the Div. of Computer Research & Technology of NIH. These data processing systems programs will be run by government personnel on the IBM System 370 under OS/MVT/HASP. A documentation viewing room will be available for three days to interested parties. A pre-proposal conference is anticipated. The location of the documentation viewing room and pre-proposal conference date will be announced in the RFP. Presently, both are planned for the second week after the release of the RFP.

It is anticipated that one award will be made as the result of this RFP. It is also anticipated that award will be for a five year incrementally funded period of performance. It is expected that the contractor shall furnish the following levels of effort per year: Year 1, 20.7 man years; Year 2, 19.7 man years; Year 3, 18.8

man years; Year 4, 17.9 man years; and Year 5, 17.0 man years.

Contract Specialist: Daniel Abbott
Cancer Treatment
301-427-8125

RFP NCI-CP-VO-91031

Title: *Holding facility for small laboratory animals*
Deadline: *May 20*

NCI is interested in contracting with at least two local organizations to obtain facilities for maintaining small laboratory animals and performing certain technical procedures relating to the animals. Facilities are needed at two locations, one in close proximity to the Frederick Cancer Research Center and at least one in close proximity to the NIH reservation in Bethesda, Md.

In addition to standard, good quality animal care, the contractors will provide virus, cell and chemical carcinogen inoculations, palpation of live animals, tumor transplantation, bleeding of live animals, routine blood work, histopathology, organ removal using aceptic technique, the administration of drugs and chemicals, and other routine services such as weighing and daily checks for mortality.

The contractor in the FCRC area will be expected to maintain approximately 8,000 mice (including 100 nude mice), 30 rabbits, 300 rats, and 500 guinea pigs.

The contractor(s) in the Bethesda area will be expected to maintain approximately 2,000 mice (including 500 nude mice), 50 rabbits, 2,000 rats, and 100 guinea pigs.

Contracting Officer: Clyde Williams
Viral Oncology & Field Studies
301-496-1781

RFP NICHD-IRP-79-16

Title: *Search for major genes which determine susceptibility to tumorigenesis caused by environmental chemicals*
Deadline: *July 2*

The Developmental Pharmacology Branch, Intramural Research Program, National Institute of Child Health & Human Development is interested in initiating research studies focusing on a search for major genes and modifier genes which determine susceptibility to tumorigenesis caused by environmental chemicals. Two dozen recombinant inbred lines and six congenic lines of mice, developed by members of the Developmental Pharmacology Branch, will be used to determine the carcinogenesis index of various polycyclic aromatic carcinogens administered subcutaneously, topically, or intratracheally.

The purpose of these studies will be (a) to understand further the importance of allelic differences at the Ah locus, and (b) to determine the importance (and number) of modifier genes (such as endogenous type C RNA virus expression, H-2 histocompatibility) with respect to interindividual risk for polycyclic hydrocarbon-induced cancers. Approximately 4,000 mice (inbred lines, progeny from the appropriate genetic backcross, R1 lines, and congenic lines) will be studied in several research protocols over a three year period.

Interested organizations must have adequate facilities and demonstrated knowledge and expertise in each of the following areas: 1. N-tropic and B-tropic ecotropic virus expression. 2. Mouse genetics. 3. Evaluation of proper "Carcinogenesis Index." 4. DNA damage and repair.

Eleanor Norment, Contract Specialist
Contracts Managment Section
National Institute of Child Health & Human Development
Landow Bldg, Room 6C29
Bethesda, Md. 20205

RFP 273-79-P0014

Title: *Biological cell line maintenance and cell culture assays*
Deadline: *Approximately May 12*

Perform tissue culture procedures for the maintenance of biological cell lines and the performance of cell culture assays of cell growth, mutagenesis and transformation. Offerors must: 1) have publications which demonstrate experience in cell culture techniques, transformation assays, scoring of morphological transformation and mutagenesis testing with mammalian cells; 2) have trained personnel available for performance of tissue culture techniques and assays; 3) have adequate facilities and equipment for performing tissue culture procedures in a sterile environment and for safe handling of chemical carcinogens; 4) be able to assure the maintenance of the viability of all cells during transport between the offeror's laboratories and the laboratories of the National Institute of Environmental Health Sciences, Research Triangle Park, N.C. (Transportation may be required on a daily basis.)

Hollis Hawkins
National Institute of Environmental Health Sciences
Procurement Office, OAM
PO Box 12874, Bldg 11 Room 1107
Research Triangle Park, N.C. 27709

The Cancer Letter _Editor Jerry D. Boyd
Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.