

THE

CANCER LETTER

P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

Vol. 7 No. 40

Oct. 2, 1981

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The Cancer Letter Inc.
Subscription \$125.00 per year

DCCP FUNDS 57 PERCENT OF EPIDEMIOLOGY R01s IN FY 1981, LESS IN 1982 BUT STILL ABOVE THE AVERAGE FOR ALL NCI

NCI's Div. of Cancer Cause & Prevention has funded 57 percent of approved competing (new and renewal) traditional (R01) grants in epidemiology and 67 percent of approved competing program project epidemiology grants during the 1981 fiscal year which ended Sept. 30.

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In Brief

SWITCH TO GRANTS DID NOT HURT VIRUS RESEARCH, WATSON SAYS; THE FIELD IS HEALTHY, WELL FUNDED

TRANSITION OF VIRUS research support from contracts to grants "is going very well. The field is extremely healthy and for the most part well funded," James Watson, a member of the Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention, reported at the Board's recent meeting. Watson said that a workshop held during the summer on viruses and human cancer delved into the questions of whether any part of the field has been hurt by the contracts to grants transition, and also on whether the search for human tumor viruses would stop. It was the opinion of workshop participants that there have been only a very few cases in which support has not been adequate; that "one of the most exciting areas now is the search for viral oncogenes—that is healthy despite the setback at Cornell," (*The Cancer Letter*, Sept. 11 and 18); and the search for new human tumor viruses is going ahead vigorously, Watson said. Some work should continue to be supported through contracts when the experiments are so difficult, with such little chance of success, that they probably would not be supported by grants, Watson commented. . . . TWO DCCP RFAs (request for grant applications) are being prepared and will be out this fall, "we hope," John Cooper, who heads the division's extramural activities, told the Board. One is for epidemiological studies of rare tumors, the other on the role of nicotine in cancer causation. The Board previously had approved the concept of those studies. . . . DCCP HAS RECEIVED three "exceptions" to the freeze on hiring from outside HHS, and has filled two of them. Peter Blumberg, from Harvard, is working in the Laboratory of Cellular Carcinogenesis & Tumor Promotion; and Kenneth Cantor was recruited from the Environmental Protection Agency to work in the Environmental Epidemiology Branch. . . . ALTON OCHSNER, among the first to link smoking with lung cancer, died last week in New Orleans at age 85. He had undergone surgery for a heart ailment at the Ochsner Medical Foundation Hospital, which he founded in 1942 and directed for 24 years. He began his studies of lung cancer and smoking in 1936 while professor of surgery at Tulane Univ., and presented his findings two years later at the meeting of the American College of Surgeons.

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DCCP EMPHASIS ON EPIDEMIOLOGY SEEN IN BUDGET; BOARD PUSHES TRAINING

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Those percentages were especially significant in a year in which DCCP funded its competing R01s overall at only 36 percent. Throughout NCI, the total was about 35 percent.

The emphasis on epidemiology within the division is further reflected by comparing those percentages with other program areas. In biological carcinogenesis (which includes virology), 36 percent of approved competing R01s were funded, as were 50 percent of program projects. The percentages in chemical and physical carcinogenesis were 34 and 44; in diet and nutrition, they were 21 and 43.

The funding percentages will drop drastically in the 1982 fiscal year, even if there is no major cut in the budget from that requested originally by the President (\$1.026 billion for NCI), or those now being considered in Congress (\$1.030 billion by the House, \$1.034 billion by the Senate).

In the new fiscal year, NCI expects to fund only 32 percent of approved competing epidemiology R01s, 33 percent of program projects. In biological carcinogenesis, it will be 28 percent and 33 percent; chemical and physical carcinogenesis, 27 percent and 11 percent; and diet and nutrition, 25 percent and 17 percent.

Epidemiology thus still fares better than the division's other programs, with an overall average funding of 28 percent for R01s and 21 percent for program projects.

The division's budget for 1982, based on the President's original request, is \$216 million, an increase of only \$2.8 million over 1981. But epidemiology goes up by \$3.6 million, to \$49.4 million. Chemical and physical carcinogenesis increases by \$4 million, to \$75.3 million; and nutrition goes up \$1.9 million, to \$8.9 million.

Those increases will come largely at the expense of biological carcinogenesis, which drops by \$6.7 million, down to \$81.8 million.

"In the past, we did not support more epidemiology grants because they just weren't there," DCCP Acting Director Richard Adamson commented. "That's changing."

Board member Bernard Weinstein said he felt the ratio of contracts to grants still is too high. Adamson responded that a new RFA (to stimulate grant proposals) in epidemiology is under consideration.

"Epidemiology still is not very strong in the United States," Board member James Watson said. "We're not doing much training. We know that epidemiology outside of NCI is not very good, so NCI has to be in the position of putting its money where it will do the most good" (Watson's point being that this encourages use of contracts).

Adamson and Joseph Fraumeni, director of the Field Studies & Statistics Program, discussed the training program which is turning out 15 epidemiologists a year. Fraumeni noted that this is in addition to the epidemiology training efforts supported by the Div. of Resources, Centers & Community Activities.

"With the new leadership at DRCCA, there will be more emphasis on epidemiology training," Adamson commented, referring to the fact that incoming Director Peter Greenwald is an epidemiologist.

Fraumeni agreed that there is "a limited pool of epidemiologists, but I disagree that a disproportionate few are cancer epidemiologists." He suggested that the Board might consider establishing a subcommittee on epidemiology to evaluate the program and make recommendations.

"We don't need to evaluate your program," Board member Hilary Koprowski said. "We need to find out why it is not better outside NCI."

"The country is training more now," Fraumeni said. "There is not yet a critical mass, but the field will catch up. There are some good programs at Harvard, in Los Angeles and in New Orleans. One problem now is that people, when they have completed their training, have no place to go. That will change in five years."

Philippe Shubik, member of the National Cancer Advisory Board who attended the meeting, suggested that "there is a need for a much bigger package. You people keep saying there are not enough people (in epidemiology), there are not enough grant applications coming in. The reason epidemiology prospers in England is that they have a national health service, with data and records readily available. It is not segregated into cancer epidemiology there. It is an error to segregate them. It is more of a problem than just needing more numbers. We need places for them to go, and availability of information."

Adamson pointed out that NCI's SEER program provides a data resource that is available to all investigators, not just those at NCI.

Donald Luecke, chief of the Special Programs Branch in the division's Extramural Program, said that a program announcement will be coming out in which medical schools and schools of public health, dentistry and osteopathy will be asked to propose individuals for special awards. "They will have a chance to gain an academic background in one area, and some will be in biometry and epidemiology," Luecke said. "The impact will be on the undergraduate level. For some medical students, it will be their introduction to epidemiology."

When Adamson pointed out that NCI funded epidemiology grants beyond the payline for other areas, Watson replied, "You possibly funded some that shouldn't be funded."

Weinstein suggested that cancer centers might be

called upon to direct more of their efforts into supporting epidemiology and the training of epidemiologists. "I've seen centers, our own (Columbia) included, shape up to meet the requirements for comprehensive cancer centers. Why should there not be a requirement that good epidemiology be included?"

"With Dr. Greenwald's appointment, that situation should be improved," Adamson said. DRCCA includes administration of the centers program among its responsibilities.

"It would be a great mistake to think that by counting on centers, the situation will be improved," Watson said. "Most of those are lousy."

The discussion ended with Adamson's comment, "It is true that epidemiologists could write better grants."

12 PERCENT BUDGET CUT WOULD CREATE HAVOC WITH NATIONAL CANCER PROGRAM

President Reagan's demand that 1982 fiscal year budgets be reduced by 12 percent from his original request would play havoc with the National Cancer Program if it is applied to NCI. So far, there has been no indication whether the Dept. of Health & Human Services will exact 12 percent cuts for each of its agencies. In past exercises of this sort, reductions have been selective and not applied across the board, but there is no assurance that will happen this time.

Reagan's budget for NCI was \$1.026 billion. A 12 percent cut would trim that amount by \$123 million, which would cut spending to less than the 1979 level. In constant dollars, NCI probably would have less to work with than it did before the National Cancer Act of 1971.

Meanwhile, the 1982 fiscal year started this week without a regular appropriations bill for HHS. Congress was expected to approve a continuing resolution—interim financing until the normal money bills have been enacted—which will permit spending at 1981 levels or the President's original budget request, whichever is lower. That will pose no problem for NCI for a month or two, but if it drags on, new programs may have to be put on hold. If the 12 percent cut is applied, there may be no new programs and some of the existing ones will disappear.

ACR PRESSES CAMPAIGN TO HAMMER HOME ADVANTAGES IT CLAIMS FOR RADIOTHERAPY

The American College of Radiology, demonstrating confidence in results of clinical studies which tend to establish radiotherapy as at least the equal of surgery in local control of some malignancies and superior in terms of organ preservation, held a seminar for the press in Washington D.C. recently to hammer home those points

Luther Brady, chairman of the Dept. of Radiation Therapy and Nuclear Medicine at Hahnemann Medical College and also chairman of the Radiation Thera-

py Oncology Group; Gerald Hanks, radiation oncologist in Sacramento and associate clinical professor of radiology at the Univ. of California (Davis); and Morris Wizenberg, clinical professor of radiology at Mercy and South Community Hospitals in Oklahoma City, presented the case for radiotherapy. The moderator was Samuel Madell, New York, chairman of the ACR Commission on Communications.

An ACR statement entitled "Radiation vs. Surgery" summarized the organization's position:

"Recent developments in therapeutic radiology have given many cancer patients a viable alternative to surgery. By selecting radiation treatment, patients are choosing a cure rate that equals, and in some cases surpasses, positive surgical outcomes while preserving an intact body and organ function.

"Radiotherapy has evolved into an extremely precise and effective technology. Once the location, size, and shape of a tumor are determined, maximum safe doses can be calculated to deliver radiation homogeneously to the designated mass without permanently disturbing surrounding healthy tissue.

"It is currently possible to give the prescribed dosage to target tissue with precision of at least plus or minus 10 percent—an exactitude unmatched by any other method of treatment. The real breakthrough came during the 1950s with the availability of electron accelerators and with the ability to produce large quantities of radioactive cobalt as radiation sources.

"By using high voltage x-rays, the radiation therapist can keep the surface dose low while maintaining uniform dose distribution in various tissues involved by the tumor. Modern accelerators are even used for treatment of very small brain lesions that are difficult to reach surgically.

"Researchers are also investigating radiation's ability to assist the body's natural immune system in fighting more generalized cancers—a function usually reserved for systemic chemotherapy. Results of studies injecting irradiated tumor cells into animals, and human treatment, indicate that radiation injured tumor cells can help the host develop increased reactivity to the tumor.

"With surgical procedures, tumor bulk is removed. But with radiotherapy, damaged tumor cells remain in place to be absorbed, thereby boosting resistance to disease.

"Some therapists believe that some of the good results which we get with radiotherapy depend on this boosting effect. If immunological reactivity of the host against a tumor is on any importance, then radiation therapy and surgery, biologically, are two different methods of treatment.

"What these technical advancements signify for the one in three people who will develop a malignant tumor during their lifetimes are greater survival rates, fewer adverse treatment effects, and better quality

of life for most cases with less functional disturbance. Summarized results from a Swedish nationwide cancer registry (begun in 1958) and recent U.S. studies affirm that after five years:

“—Ninety percent of the patients with laryngeal cancer detected in early stages are cured with preservation of larynx and vocal cords.

“—Ninety percent of the patients given adjuvant radiation therapy following removal of a seminoma from the testicle are cured, versus under 50 percent without this additional treatment.

“—Eighty percent of the patients with Hodgkin's disease discovered in early stages survive with radiotherapy, while less than 20 percent survived prior to development of this therapy.

“—Fifty percent of the patients receiving radiotherapy following early kidney cancer surgery are cured, as opposed to seven percent with surgery only.

“—Seventeen out of 20 patients with retinoblastoma, an eye tumor, are cured with eye and vision preservation.

“—Sixty-70 percent of the patients diagnosed with prostate cancer limited to the gland are cured with surgery compared to 95 percent survival rate for those having the same diagnosis followed by radiotherapy, and 60-75 percent survival rates for all cases.

“—Eighty percent of the patients with early breast cancer are rehabilitated—a figure comparable to surgical management.”

Brady presented data on radiotherapy for breast cancer and blasted what he called the “wham bam” single step biopsy-mastectomy procedure as a “travesty.”

“There have been data available for some time that demonstrate, without question, that one can cure cancer of the breast by definitive or curative radiation therapy techniques, with figures that are essentially equivalent to what can be achieved by surgical management,” Brady said.

The five-year, disease free survival rates he cited for women who undergo radical or modified radical mastectomy are: 84 percent for stage 1 cancer, which has not spread to the lymph nodes or axillary glands; and 66 percent for stage 2 cancer, which does involve the lymph nodes and axilla. A 1977 study shows the five-year survival rate of women treated with radiation as 81 percent in early lesions and 60 percent for advanced lesions. The 1977 data demonstrate the survival statistics when the lump is left in place, Brady pointed out.

The cure rate for radiation therapy today is higher than that shown in the 1977 study, Brady said, because “we've learned more now, that one needs to remove the lump in the breast in toto by excision, rather than by incision.” The results of that technique were reported in *The New England Journal of Medicine* in July 1981 (Vol. 305, No. 1, pp. 6-11;

Veronesi et al). In a controlled clinical trial involving 701 patients identical survival was achieved with radical mastectomy or excision plus radiation therapy.

It is especially crucial that women and their physicians be aware of radiation therapy as a treatment alternative, because the trend toward early detection is bringing in more women who are candidates for radiation therapy, Brady said.

“In 1980, stage 0, or in situ noninvasive cancer of the breast, was found in 10 percent of all women with cancer of the breast, and 57 percent of all women are now presenting with stage 1 disease limited to the breast. As a consequence, we can give to the women with the earlier diagnosis the possibility of treatment with preservation of the breast intact and with appropriate and good cosmetic results. That is an important, dramatic, and major consideration because saving of the breast does not decrease the likelihood of survival,” Brady said.

Many women who could benefit from radiation therapy are denied the opportunity to choose this treatment, Brady contended. The family physician who first examines a lump in a woman's breast may be ignorant of radiation therapy as a viable treatment alternative—or he or she may be reluctant to advise any treatment but mastectomy if the lump is found to be malignant.

“Too often,” Brady said, “a woman who discovers a lump in her breast is given the wham-bam treatment. In 24 hours she's in the hospital on the table having the lump removed, with permission signed that if it's malignant, she's going to have the breast removed either by radical mastectomy or modified radical mastectomy or total mastectomy. No emphasis is given to knowing if this is a limited local disease process, or if it's part of a disseminated widespread disease process. That is a travesty.”

Another problem, Brady pointed out, is that many modified radical mastectomies are performed by surgeons “without a great deal of experience, who have not been trained in that area, and who don't do it well,” resulting in a greater frequency of local or regional recurrence of the cancer.

The best approach to treatment, Brady maintained, begins with a diagnosis established by excision of the lump, giving the pathologist adequate time to look at the tissue sections on permanent slides. This should be followed by a thorough work-up to determine the extent of the disease process—whether it's limited and local, or widespread and disseminated. “That just doesn't happen in this country, and it should. It allows time for the woman to have a better understanding of the problem and to participate in the decision relative to her management. And, if appropriately done with both physicians present at the same time, the surgeon and the radiotherapist, the best decision can be made for

management without any compromise in the outlook for the future."

The American Cancer Society estimates that one out of every 11 women in the U.S. will develop breast cancer. According to Brady, one out of every 10 patients who died of cancer in 1980 was a woman with breast cancer.

"We think the situation can be improved," he said. "Statistics show that the earlier breast cancer is detected, the better the patient's chance for survival. Many women who know they have a breast lump delay until it's too late because they fear the treatment almost as much as they do the disease. Knowing that there is effective treatment which can both cure the disease and save the breast offers an opportunity to change the outlook in breast cancer."

Hanks described the **Patterns of Care Study**, a project initiated in 1974 to examine the practice of radiation therapy in the U.S. and to improve the quality of cancer care.

The PCS is totally funded by NCI and is administered by ACR through its Radiation Oncology Study Center in Philadelphia. A major goal of PCS is not only to document survival rates, but also to determine what factors influence patient outcome, and how radiation therapists can improve their practice. Radiation therapists are the only medical specialists who have organized such a comprehensive self appraisal, ACR pointed out.

One facet of the Patterns of Care Study is an Outcome Study to evaluate and document the results of treating various cancers with radiotherapy. The Outcome Study so far has provided reports on national results of radiotherapy in six disease sites: tongue and floor of the mouth; larynx; cervix; Hodgkin's disease; seminoma of the testis; and prostate.

Hanks is chairman of the Outcome Study and one of the authors of the study's report on prostate cancer. That report claimed that patients with stage A prostate cancer treated with radiation had a 91 percent survival rate, that three year survival for patients with stage B was 88 percent, and for stage C it was 76 percent.

(A detailed report on the Outcome Study's findings on prostate cancer appears in the September issue of *The Clinical Cancer Letter*, along with comments by Gerald Murphy, chairman of the National Prostatic Cancer Project, who disputed some of the radiotherapists' claims favoring radiation over surgery.)

Hanks pointed out that the Outcome Study on prostate, like other PCS outcome studies, was designed so the results would be representative of the national practice. He also reported that the study has resulted in specific recommendations for radiation oncologists that can optimize treatment and improve patient outcome.

Hanks said that findings of the outcome study on prostate include:

- Patients undergoing a transurethral prostatic resection (TURP) for diagnosis or relief of obstruction have an increased risk of recurrence of the disease. The study suggests a TURP may cause the disease to spread.

- Patients treated at institutions having linear accelerators had a slightly lower recurrence rate than those treated elsewhere.

- Physicians practicing radiotherapy on a fulltime basis usually performed more in keeping with what is considered best current management than those practicing parttime.

- Patients treated within the PCS limits on dose, treatment time, and field size had lower recurrence rates than those who weren't.

- Significant prognostic variables identified in the PCS Outcome Study, in addition to stage of disease, include tumor grade, age of patient, serum acid phosphate level, prior hormone therapy, and general health index.

- The national results (all types of practice) are equal to those reported from major academic institutions; therefore, the private practitioner and the community hospital are performing very well in managing prostate cancer.

PCS evolved from the ideas and concerns of two men, Hanks noted. Simon Kramer, professor and chairman of the Dept. of Radiation Therapy and Nuclear Medicine at Thomas Jefferson Univ., is principal investigator and director of PCS. David Herring, a La Jolla physicist, provided much of the conceptual design of the study.

Kramer and Herring wanted to investigate whether the level of clinical care could be quantified, and what aspects of the environment in which radiation therapy is practiced most influence the quality of care. The first survey identified 1,216 fulltime radiation oncologists in 1974, and demonstrated that nearly 50 percent of cancer patients receive some form of radiation treatment.

One of the first major accomplishments of PCS was to establish a consensus on the best current management (BCM) for 10 specific types of cancer, Hanks said. Panels of 50 senior therapists analyzed the characteristics and treatment of the different tumors and then constructed a "decision tree" for each one. This is a chart that shows the logical succession of key treatment decisions to be made by the physician.

Information and insights gained from PCS studies are routed back to the radiation therapy community by means of newsletters, conferences, seminars, exhibits at scientific meetings, audiovisuals, and self teaching modules.

"I think everybody touched by the study has been improved," Hanks said. "Everybody I've talked to

has changed the way he's practiced after contact with PCS. That might be the biggest single impact of the study."

SCIENTIFIC PROGRAM ORGANIZED, XIIIth CANCER CONGRESS WILL BE "MEMORABLE"

The XIIIth International Cancer Congress will be "a memorable one by providing a thoughtful and imaginative program of interest to a broad spectrum of physicians, dentists, scientists, nurses, social workers, health professionals and lay personnel from volunteer organizations" engaged in cancer related activities, Congress President William Hutchinson, Secretary General Edwin Mirand, and National Program Committee Chairman Enrico Mihich wrote in a special Congress issue of the UICC *Cancer Bulletin*.

The National Program Committee has invited submission of abstracts of papers intended for presentation at the Congress.

The deadline for submission of abstracts is Dec. 1, 1981.

The scientific program will include 10 plenary lectures by distinguished individuals on timely subjects. The format also includes:

—General symposia on cellular and molecular events during carcinogenesis; gene expression and its regulation; concepts in chemotherapy; recent advances in clinical cancer immunology; advances in di-

epidemiological developments, late consequences of cancer therapy, pain control in the management of the cancer patient, genetic susceptibility to cancer, childhood tumors, screening for cancer, microsurgery and myocutaneous flaps in tumor surgery, imaging techniques for detection and extent determination of cancer, the pathology of incipient neoplasms, oncological emergencies, nutrition and cancer management, hyperthermia, cytogenetics and cancer, nutrition and cancer causation, application of basic concepts to clinical chemotherapeutic design, hospice: the concept and role, cancer nursing: an international perspective, and economics of cancer care.

PROGRAM ANNOUNCEMENT

Experimental Research Related to Biological Effects of Low Doses of Ionizing Radiation

The Low Level Radiation Effects Branch of NCI is inviting grant applications for the purpose of encouraging cellular and animal studies that will provide new and relevant information on the molecular and cellular processes leading to mutagenesis, cell transformation, and carcinogenesis by low doses of ionizing radiation.

Uncertainties in the risk estimates for human cancers and mutation are due to our lack of understanding of the basic principles of radiation mutagenesis, carcinogenesis, and cocarcinogenesis. The area of mutagenic and carcinogenic mechanisms was

mechanism of mutagenesis (transition, transversion, frame-shift, deletion, etc.) differs depending on the locus under study and the nature of the mutagenic agent.

A number of controllable variables can be exploited in the study of the processes that lead to radiation-induced mutations. In mammalian cells, for example, different loci have been found to be sensitive to mutagenesis at different phases of the cell cycle. Mammalian cell lines with useful genetic properties, such as DNA repair defects, are available and are suitable for studies on mutation mechanisms. Continued research is needed in the development of suitable cell lines. Variables such as dose rate, radiation quality (usually expressed as linear energy transfer, LET), chemical sensitization and protection, DNA repair perturbation, etc. may be used as variables in experiments designed to characterize the mutation process.

It is expected that the research will emphasize cellular and molecular studies. An understanding of the basic mechanisms of mutagenesis may permit the construction of models which could predict the incidence of mutations in human beings following a given exposure to ionizing radiation. The extrapolation of laboratory results to human populations is an important goal of the research on radiation mutagenesis and is considered necessary for the successful assessment of genetic risks in human beings.

B. Radiation-Induced Cell Transformation

Of all the biological effects of ionizing radiation, carcinogenesis is presently of the greatest concern. Heightened awareness of environmental carcinogenic agents in general has made neoplasia the most widely feared result of radiation exposure. Epidemiological studies of irradiated human populations and a wide variety of studies on experimental animals clearly indicate that radiation causes cancer. It has long been recognized that animal data alone cannot be used to make quantitative predictions for the number of human cancers expected to be induced by radiation. However, animal and cellular data can provide information on general principals and mechanisms of radiation effects. Predicting dose response relationships at low doses and dose rates must depend upon understanding the phenomena that give rise to these functions.

Transformation toward malignant behavior can be induced in animal cells in culture by a number of different agents, including radiation, viruses, and certain families of chemicals. While it is important that research continue to determine the relationship between cancer in vivo and cell transformation in vitro a number of specific research needs in radiation carcinogenesis using cell transformation in vitro can be identified. In vitro transformation represents one of the most sensitive mammalian systems for the study

of radiation responses and requires only a few weeks for an experiment, compared to months or years required for tumor expression.

C. Radiation Carcinogenesis in Animals

The carcinogenic risk to human populations exposed to low doses of ionizing radiation may depend largely upon other environmental factors. For example, a possible correlation exists between cigarette smoking and the induction of lung cancer by alpha radiation, and certain agents can strongly enhance cellular transformation in vitro and tumor induction in animals. "Initiation" and "promotion" are considered steps on the way to the neoplastic state; other steps may exist. Ionizing radiation can apparently act as both initiator and promoter. Host factors are known to be paramount in animal tumor production: oncogenic virus genes, the immune system, hormonal status, and inherited DNA repair capacity. In order to evaluate radiation as an initiator and/or promoter of cancer the role of other chemical and biological factors need to be explored as well. It will therefore be necessary to integrate effectively radiation biological data with the greater body of knowledge concerning carcinogenesis.

The sensitivity to radiogenic cancer among different organs and tissues varies with the strain or species of animal studied. This fact should be useful in the study of the host factors controlling sensitivity (or resistance) to radiation-induced cancer and eventually help lead to an understanding of what may be large differences in radiation sensitivity among individuals in a heterogeneous human population.

The rate and manner in which a radiation dose is delivered has profound influence upon the carcinogenic response in animals. As dose rate is decreased, the slope of the dose response curve for low-LET radiation is more reduced and approaches a limiting low value. High-LET radiation is more effective than are X and gamma rays in the malignant transformation of cells in culture and in the induction of tumors in animals. Research is needed on the influence of these variables on the carcinogenic response and the mechanisms involved.

D. Approach

The applicant is encouraged to consider promising areas of research that may lead to the prediction of mammalian and human dose response relationships at low doses and dose rates. The application should deal with any of the various steps involved in mutagenesis or the induction of neoplasia. The roles of molecular damage and its repair, the differentiated state of affected cells, organ-specific reactions to transformed cells, tumor promoting events, the immune response, endocrine status, and environmental and intrinsic factors other than radiation are to be considered. Proposed experiments should be designed to produce information that can be used in the de-

velopment of a conceptual framework that predicts a priori what form dose response functions will have at low dose and at low dose rate.

Specific research needs are considered to exist in the following areas:

—The correlation of the biological endpoints (mutation, transformation, carcinogenesis) with chemically defined lesions in DNA or other structures.

—The understanding of "single hit" or linear dose effects, their possible dependence on dose rate, and how they are influenced by molecular and cellular repair processes.

—Investigations that determine the functional significance of radiation-induced chromosome anomalies with respect to mutagenesis and carcinogenesis.

—Determination of the relationships between cell transformation in vitro and tumor induction in vivo.

—The development of cell and animal systems with properties that permit the study of the role of specific molecular processes in mutagenesis and carcinogenesis, such as radiation sensitive, repair deficient, and other specialized strains of cells and animals.

—Studies on promoting and modifying conditions that may form the underlying bases for variations in susceptibility to cancer induction.

The mechanism of support will be the traditional research grant. Policies that govern the research grant programs of NIH will prevail. The award of grants pursuant to this program announcement is contingent upon receipt of proposals of high scientific merit and the availability of appropriated funds.

Applications will be accepted on or before the usual dates for new applications on an indefinite basis: March 1, July 1, and Nov. 1.

Applications should be submitted on Form PHS-398, which is available in the business or grant offices of most academic and research institutions or from the Div. of Research Grants, NIH.

The phrase "Prepared in Response to NCI Announcement on Biological Effects of Low Doses of Ionizing Radiation" should be typed across the top of the application. The original and six copies should be sent or delivered to: Application Receipt Office, Div. of Research Grants, NIH, Room 240, Westwood Bldg., Bethesda, Md. 20205.

In order to alert the Low Level Radiation Effects Branch to the submission of proposals as requested above, copies of the face page and summary page of such applications should be forwarded under separate cover to: Dr. Oddvar F. Nygaard, Low Level Radiation Effects Branch, NCI, Room 4B29, Bldg. 31, Bethesda, Md. 20205.

RFA Grants in Nutrition

NCI—Training

The National Cancer Institute invites applications for institutions grants for National Research Service Awards (NRSAs) in nutrition as it relates to cancer cause, prevention, detection, diagnosis, treatment, and restorative care. Proposed projects may encompass both predoctoral and postdoctoral research training, or may support postdoctoral training only. The first deadline for receipt of applications is Feb. 1, 1982. Those applications will be reviewed by the Cancer Research Manpower Review Committee at its scheduled meeting in May, 1982, and by the National Cancer Advisory Board at its scheduled meeting in October, 1982. Qualifying applications will be considered for funding thereafter, in accordance with the usual NRSA receipt dates of Feb. 1, June 1 and Oct. 1.

The current NIH definition of nutrition as it applies to this effort is:

"The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular and subcellular level. This definition also includes:

"Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.

"All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.

"Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."

Applications should be submitted on Standard Form PHS 6025. At the top of the first page of said application form the applicant should type in capital letters "Submitted in Response to Nutrition Program Announcement." Before writing and submitting applications, applicants should discuss their plans with NCI staff and should request a copy of the NCI Guidelines on Cancer Orientation in Research Training Grants. The NCI staff representative is: Barney C. Lepovetsky, PhD, JD, Chief, Research Manpower Branch, Div. of Resources, Centers & Community Activities, Blair Bldg., Room 717, 8300 Colesville Rd., Silver Spring, Md. 20910.

The Cancer Letter — Editor Jerry D. Boyd

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