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HOUSE OVERRIDES VETO OF AUTHORIZATION BILL AS GOP MEMBERS JOIN DEMOCRATS IN ASSAILING REAGAN ACTION

President Reagan's veto Nov. 8 of the Health Research Extension Act of 1985, which included renewal of the National Cancer Act, was resoundly overridden by the House of Representatives Nov. 12, 380-32, far more than the two thirds vote required. The Senate was scheduled

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In Brief

LANE ADAMS RETIRES, GADBERRY NEW EXECUTIVE VP; LEMAISTRE ACS PRESIDENT, LOEB PRESIDENT ELECT

LANE ADAMS, who has been executive vice president of the American Cancer Society since 1960, will retire in January. His replacement will be Robert Gadberry, 67, Wichita public relations consultant and former chairman of the ACS national Board of Directors. Gadberry has been a delegate director to the national board for 20 years, and headed the ACS crusade in Kansas in 1968-69. Under Adams' leadership as chief staff officer, ACS grew from $30 million in contributions in 1960 to $250 million this year, with 3,200 local affiliates, two and a half million volunteers and 3,000 paid staff. The Society supported $70 million in cancer research this year.... **CHARLES LEMAISTRE,** president of the Univ. of Texas System Cancer Center, was elected national president of the American Cancer Society at the organization's annual meeting last week. LeMaistre said prevention of cancer will be emphasized during his tenure. Virgil (Bud) Loeb, professor of clinical medicine at Washington Univ. and an international leader in cancer treatment and clinical research, was elected vice president and president elect. . . . **MORTIMER LIPSETT,** 64, director of the National Institute of Arthritis, Diabetes & Digestive & Kidney Diseases since January, died Nov. 10 of cancer at the NIH Clinical Center. Former director of the National Institute of Child Health & Human Development, Lipsett also served as director of NIH's Clinical Center. He was the first chairman of the Breast Cancer Task Force, an authority in endocrinology, and recipient of numerous awards, including the Alfred P. Sloan Award for Cancer Research. Lipsett joined NIH in 1957 and became NCI's endocrinology branch chief in 1966.... **OTIS BOWEN,** former Indiana governor and professor of family medicine at Indiana Univ. School of Medicine, has been named by President Reagan to replace HHS Secretary Margaret Heckler. His appointment requires confirmation by the Senate. Orrin Hatch (R.-Utah), chairman of the Senate Labor & Human Resources Committee which will hold a hearing on the nomination, said Bowen "is exceptionally qualified" for the job and his "expertise and sound judgment will come in handy" at the department.

HOUSE OVERRIDES VETO AS GOP MEMBERS HINT WHITE HOUSE RENEGED ON DEAL

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to act on the veto Nov. 13, after **The Cancer Letter's** press time. Sen. Orrin Hatch (R.-Utah), coauthor of the bill along with Congressman Henry Waxman (D.-Calif.), had determined after the veto that he would lead the effort in the Senate to override it, difficult as that may be for a leader in the President's party to do.

There was never any doubt that the House would hand Reagan a one sided defeat on the override. Minority Leader Robert Michel, who as the ranking Republican on the House Labor-HHS Appropriations Subcommittee had usually supported more generous funding of NIH and NCI than various administrations requested, virtually invited Republican members to vote against their President. He noted that in his position as a party leader it was almost mandatory for him to vote to sustain the veto, "but my heart won't be in it. Of all those measures which have come down the pike that are candidates for veto, this is the least of them," Michel said.

In his veto message, Reagan insisted his action "in no way should be interpreted as lessening our commitment to the endeavors of the National Institutes of Health." However, the measure "would impose numerous administrative requirements which would interfere with carrying on research activities in the most cost effective manner. It would diminish administrative flexibility. It is overloaded with objectionable provisions that threaten NIH's capacity to manage itself."

Included in the legislation, and cited last year as one of the reasons why he pocket vetoed it then, is the creation of a National Institute of Arthritis and Musculoskeletal Diseases. In an about face on that issue, Reagan said in the veto message that he had directed the secretary of the Dept. of Health & Human Services to establish the new institute administratively. But, he said, creating a National Center for Nursing Research at NIH, also in the bill, is not acceptable because it does not fit into the mission of NIH.

Waxman, chairman of the Health Subcommittee of the Committee on Energy & Commerce, was joined by Edward Madigan, the ranking Republican on that subcommittee in urging a vote to override. Waxman noted that the bill passed the House by a 395-10 vote, and that it was a "bipartisan compromise after three years of hearings and debate... The issue is not over money, but over whether Congress should have a say on how $5 billion a year in taxpayers' money should be spent, whether Congress should have a say in establishing priorities."

Madigan pointed out that the legislation was a compromise which had been worked out between the House, Senate and White House, and noted that 78 senators had a signed a letter urging the President to sign the bill. He refuted Reagan's contention that the bill was virtually the same as the one he vetoed last year, noting that the authorization time had been changed to three years, the nursing institute had been downgraded to a "center," that the requirement to support at least 55 cancer centers had been dropped, and that provisions relating to manpower training had been changed, all at the request of the Administration.

Michel elicited from Madigan a restatement of the fact that the Administration had been consulted in crafting the compromise, particularly in discussions between Hatch and Administration representatives. "Then notwithstanding all the efforts to accomodate the Administration," Michel said, "it seems very odd that there should be a recommendation for a veto. Can you enlighten us on that?"

Madigan said that a representative of the Office of Management & Budget who had not previously been involved in the negotiations expressed concerns about "micromanagement" of NIH by Congress. Madigan indicated those concerns had to do with restrictions on fetal research and requirements for handling laboratory animals, and on expediting peer review to meet emergency situations. Without those provisions, Madigan said, "it would not have been possible to pass a bill without a closed rule (forbidding amendments)."

Other comments made during the "debate" (in which not a single member supported the veto):

Ron Wyden (D.-Ore.)—"In the veto, the Administration is running up a white flag in the war against Alzheimer's disease and cancer. The investment in research has paid off handsomely."

Howard Nielsen (R.-Vt.)—"The micromanagement issue was overstated. A lot of bills should have been vetoed, but not this one."

Harold Ford (D.-Tenn.)—"At the current rate of investment, we cannot meet NCI's goal for reducing cancer mortality 50% by the Year 2000."

Doug Walgren (D.-Pa.)—"This essentially is a battle over whether Congress has anything to say about NIH and whether we can bring back from our districts the concerns of citizens."

Carl Pursell (R.-Mich.)—"The veto was based on the nursing center and congressional intrusion into NIH management. Neither is valid. The veto is an unfortunate decision, considering the reasons"

Dennis Eckart (D.-Ohio)—"The bill is fiscally resonsible. We placed a ceiling on (indirect costs), emphasized prevention and consolidated some burdensome, unnecessary reports."

PB-8511-018192

NCI SUPERCOMPUTER TO BE OPERATIONAL BY MID APRIL AT FREDERICK CAMPUS

NCI's new supercomputer will be operational by the middle of April, Jacob Maizel, chief of the Div. of Cancer Biology & Diagnosis' Mathematical Biology Laboratory, told **The Cancer Letter.**

To be located at the institute's Frederick Cancer Research Facility, the highspeed computer will be the first supercomputer designed for and devoted primarily to research in the biomedical sciences. NCI recently signed an $11 million contract with Falcon Systems that includes the cost of the supercomputer itself, at least five front end computers to connect to the supercomputer, as well as installation, service contracts and training. The supercomputer was built by Cray Research. NCI plans to initially install three or four APOLLO computers to connect to the system, and two VAX high speed computers, a VAX 785 and VAX 8600. The VAX computer is made by Digital Equipment Corp.

NCI plans to link a computer in DCBD's Laboratory of Mathematical Biology with the front end of the supercomputer at FCRF; a proposed second line would be available to link NIH's Div. of Computer Research & Technology or other computers.

NCI Director Vincent DeVita has estimated that NCI investigators will use approximately one third of computer time on the new supercomputer, with another third of the time used by NIH, and the remaining third to be used by investigators outside NIH. NCI has not yet established dollar fees for use of the system, but officials expect to eventually initiate a fee recovery system for use of the computer.

A formal application procedure for use of the supercomputer by outside investigators has not yet been established, either. Investigators interested in using the supercomputer should contact Jacob Maizel at 301-496-4781.

According to background material from the institute, a supercomputer may be 30 to 150 times faster than the widely used high speed computer VAX 11/780 for biomedical applications such as sequence analysis. "The best way to discover relationships between genes is through their nucleic acid and protein sequences," it says, adding, "an example is the relationship of platelet derived growth factor and the 'sis' oncogene product." Published nucleic acid sequences are entering the Genbank collection at a rate in excess of 100,000 bases per month from journals. Noting that the current size of the collection is 2.8 million bases, the paper says, "A highly desired and essential analysis is to compare all new sequences with existing ones that detect subtle relationships indicative of functional relationships between genes and their products, if we are to understand the complex interaction of macromolecules in normal and abnormal cells."

To compare the sequences by the "most thorough" programs currently in use would require dozens of typical research computers working continuously, it maintains. For example, the VAX 11/780, often regarded as the standard for comparison, would require about 30,000 hours or 40 VAX equivalents of time per month. Even quick programs that skim through the data in various ways would take hundreds of hours each, but that is only half the problem because some of the most important analyses use the protein sequences derived from nucleic acids. Since there are spliced genes, overlapping genes and genes on either DNA strand this must be done for all possible translations, leading to some 200,000 amino acid residues to search per month. The problems are similar but somewhat more sophisticated for detecting protein relationships, it says. At minimum, the time needed would be double.

A supercomputer is typically 30 to 150 times faster than a VAX and could perform these analyses fast enough to keep up with the published data. Its first priority would be to examine the estimated tens of thousands of bases per month of newly determined sequences being generated at NCI and NIH, the paper says. These should be analyzed in the fullest possible detail before they are published.

The prediction of RNA secondary structure is another computationally intensive area of increasing importance. This property is important for regulation of expression and processing of mRNA and interactions between proteins and nucleic acids. The only computer currently suitable for these calculations on most mRNAs is a VAX in the National Institute of Child Health & Human Development.

X-ray crystallography is another area in which computation is "of proven and increasing importance that is expanding rapidly." As research becomes more and more active, driven in part by the need to obtain pure materials for crystals, molecular cloning promises two contributions to this research. One is the ability to produce quantities of pure proteins that are otherwise impossibly scarce and the other is the possibility of altering their sequence under the combined guidance of molecular biologists and crystallographers. These capabilities will allow enormous expansion of knowledge on structure and function of proteins, it says. "As the knowledge grows and the ability to look for relatedness in three dimensions develop through the use of stronger computers, we can expect more and more success at understanding molecular oncology and other molecular diseases."

Molecular dynamic calculations are another biomedical research application in which the supercomputer will have "immediate impact," according to the background paper. The computation methods are similar to those of crystallography except that thousands are needed to cover the steps needed to represent significant transitions from one molecular state to another. The technique involves moving all the atoms of a single structure step by step as predicted from classical laws, taking into account changes in times and interatomic forces, in order to make "dramatic movies" of the opening and closing of catalytic sites and the writhing of protein chains. Similar methods are used to predict how drug molecules interact with proteins and how a modified protein sequence would differ from its parent.

Methods similar to those of molecular dynamics can be used for three dimensional graphic analysis of proteins. The use of a supercomputer will increase computation and transfer of data by 50-100 fold, it estimates.

The speed of the supercomputer is also expected to greatly facilitate analyses of large digital images obtained from radioautograms, light micrographic images of cells, electron micrographs of cells and molecules, and Fourier analysis of images that need speeds that can't be obtained on ordinary machines.

The supercomputer is also expected to be useful for the rapid analysis of large databases of patient information, clinical observations, mutations, sequences, two dimensional and three dimensional images. In addition to its fast central processor, a supercomputer has a number of special processors that move data very fast from discs to core memory. The speedups are large, and vary depending on the exact applications.

PB85-118793

RECOMPETITION OF CONTRACT FOR STUDIES OF OLD WORLD MONKEYS APPROVED BY BSG

NCI's Div. of Cancer Etiology has approved the recompetition of two contracts for tumor promotion and transplacental carcinogenesis in old world monkeys. Currently held by Meloy Labs, the contracts will be combined into a single contract. The four year, $1.887 million project has a proposed first year funding of $437,953.

DCE's Board of Scientific Counselors unanimously approved the concept, but with the condition that studies be limited to cases in which the nonhuman primate represents the closest model to humans. Board member Renato Dulbecco expressed concern about using primates for general research instead of specific research in which the monkeys are a necessary animal model. Fellow board member George Vande Woude suggested that use of the primates be restricted to cases in which a specific model is useful.

DCE Director Richard Adamson stressed the biological rationale for using primates, particularly in transplacental studies. Although primate studies can validate observations in a rodent model, investigators can't extrapolate transplacental carcinogenesis from rodents to humans, he emphasized. "I am a critic of jumping from mouse to man in regulatory actions," he said. "I think you need something a little better." Adamson cited birth defects associated with thalidomide as an example of the need for animal models with a closer relationship of the placenta to humans, noting that FDA didn't observe any problems in rodents receiving the drug.

Industrial chemicals that may cause chronic and consistent bone marrow depression in humans are another example of studies in which a rodent model is inadequate, he said. Jerry Rice, chief of DCE's Laboratory of Comparative Carcinogenesis, stressed the importance of studying long lived animals vs. short lived ones.

Board member Donald Davies acknowledged that the similarity in biology between monkeys and humans is important, but added that he would still recommend careful control of the project. Board members endorsed a suggestion by Janet Butel that the studies involve only the minimum number of animals necessary. Adamson told the board that a statistician can be employed to ensure that only the minimum number of primates necessary for statistically sound studies are used.

The board also stipulated that reviewers at the next site visit to the facility be made aware of the group's concerns about the project.

The project combines current contracts for transplacental carcinogenesis and tumor promotion in the patas monkey, and tumor promotion in cynomolgus monkeys. The current contract for patas monkeys was competitively awarded in 1972. The closed breeding colony now consists of approximately 185 patas monkeys.

Originally established in September 1982, the contract for cynomolgus monkeys supports a colony of 100 animals for exploratory studies to determine whether the species may be more useful for initiation/promotion than the patas, in view of its human like ability to repair DNA damaged by carcinogens and the extensive dose/effect relationships for carcinogenesis by nitrosamines that have been previously established for the species by other investigators. The board approved NCI's request to noncompetitively extend the contract for nine months in order to bring it into phase with the patas contract so the two can be combined into a single contract.

Planned future studies under the project are designed to balance short term vs. long term experiments so that the size of the colony remains constant. Long term studies in transplacental carcinogenesis will include continuing observation of carcinogen treated monkeys for tumor development, including more precise definition of periods of maximal susceptibility for direct acting alkylating agents; for metabolism dependent carcinogens that have short lived reactive intermediates; and for metabolism dependent agents that have relatively stable reactive metabolites.

New emphasis will be placed on studies of compounds and phenomena expected to be of direct relevance to evaluation of human risk. This includes expansion of transplacental studies to include tobacco specific nitrosamines; determination of persistence in placental DNA of adducts of environmental carcinogens and evaluation of the utility of placental DNA adducts as markers for transplacental exposure to carcinogens.

Other concepts for recompetition of contracts approved by the board were:

Laboratory rodent and rabbit facility as a resource to the Laboratory of Cellular Carcinogenesis & Tumor Promotion. Recompetition of a contract now held by Microbiological Associates. Estimated first year award, $400,515, four years.

The Laboratory of Cellular Carcinogenesis & Tumor Promotion plans, develops and implements a comprehensive research program to determine the molecular and biological changes which occur during the process of carcinogenesis. The model for induction of squamous cancer by chemicals, mouse epidermis, is utilized in both in vitro and in vivo studies. Cell culture experiments are designed to define the normal regulatory mechanisms of epidermal growth and differentiation and to determine the mechanisms by which carcinogens, tumor initiators and tumor promoters alter this regulation. In vivo experiments are then performed to correlate, validate and extend the in vitro findings. Other in vivo experiments are designed to better define the biology of the process of carcinogenesis, indicting new agents or treatment protocols for in vitro studies. The coordinated research program of LCCTP requires both in vivo and in vitro experimental approaches. Since no animal care facilities are available in Bldg 37 at the present time, the use of a contract facility is necessary.

The function of this contract is to provide space, care and technical support for the conduct of in vivo experiments. The contractor shall:

1. Provide proper housing and husbandry for the maintenance of healthy intact and nude mice, vitamin deficient hamsters and normal rabbits.
2. Monitor animal health through periodic testing for pathogenic viruses, bacteria and parasites.
3. Provide a hazard free environment to safely conduct skin carcinogenesis experiments using initiating and promoting chemicals.
4. Maintain a barrier environment for nude mice to be used for homograft and xenograft experiments and tumorigenicity testing of a variety of cell lines by injection or implantation.
5. Prepare diets for vitamin deficiency studies and monitor animal weights and other clinical signs of deficiency states.
6. Conduct skin painting experiments, including application of chemicals and counting of tumors and gross autopsies.
7. Perform skin grafts on nude mice.
8. Inoculate rabbits and other species with antigens provided by NCI, bleed inoculated animals and collect antiserum.

Henry Hennings is the project officer.

Conventional laboratory rodent facility. Recompetition of a contract currently held by Microbiological Associates. Estimated first year award, $350,000, four years.

This contract was established competitively to support the intramural Laboratory of Comparative Carcinogenesis research program by providing a facility for conducting carcinogenesis studies in species, strains, or lines of rodents that are not obtainable as pathogen free products of the Frederick Cancer Research Facility animal production area. Such conventional rodents cannot be used in the animal research facilities available to LCC at FCRF. During the period January-June, 1985, this contract supported 23 projects involving 14 LCC investigators, and in June, housed approximately 930 rats, 680 mice, 150 gerbils, and 160 hamsters. It has been used in the past for exploratory studies in Sencar and strain A mice and in Syrian hamsters, all of which have subsequently become available at FCRF, and for one time experiments in ACI rats, in B10.A and in other congenic strains of mice, and in Mongolian gerbils, which preliminary studies indicate would not be of recurring usefulness and which were therefore not proposed for introduction into FCRF. The availability of this facility makes possible exploratory studies that require commercially available animals, in a timely manner. Recompetition of this effort is requested for four years at a decreasing level of funding during which a major fraction of the effort supported by the contract is expected to shift to FCRF.

This project provides support for studies on transplacental carcinogenesis and on cellular specificity and structure/activity relationships for tumor promotion in nonsquamous epithelia, and is expected to increasingly support mechanistic studies on carcinogenesis by salts of heavy metals, including Cr, Ni, Pb, and Cd. The contract allows use of strains of rats and mice for which there is an existing data base for carcinogenicity studies, but which are only obtainable from commerical (non-FCRF) sources. This is especially true of the outbred Wistar rat, with its low natural incidence of Leydig cell tumors and its high susceptibility to cadmium.

The rodent facility will house animals that have been exposed to carcinogens by gavage, injection, or

topical application. No carcinogen feeding studies will be performed. Promoters, such as phenobarbitol, may be given in drinking water. All experimental protocols are provided by the project officer and carried out by the contractor. The contractor will administer carcinogens, maintain and observe the animals, record observations, and perform necropsies. Histologic slide preparation, histopathology review, and biochemical investigations on tissues from animals under study will be performed by NCI scientists at FCRF. The contractor will provide monthly reports on progress of each experiment and will frequently consult with the project officer and LCC investigators.

Jerrold Ward is the project officer.

Ethylene oxide mortality study. Recompetition of contracts held by Dynalectron Corp., Stokes Services and Equifax, supported through the NCI/NIOSH interagency agreement. Estimated first year award, $122,100, three years.

Ethylene oxide (EtO) is used as a sterilant in the health care and food industries, and as an intermediate in the production of a number of chemicals. The largest population of workers exposed to EtO is is involved in the sterilization of medical supplies, and NIOSH has estimated that 75,000 workers are potentially exposed to EtO in the health care industry. Cytogenic studies of animals and humans have consistently demonstrated an excess of chromosomal aberations. In two inhalation studies of rats exposed to EtO an increased incidence of mononuclear cell leukemia, brain cancers and peritoneal mesotheliomas were reported. Epidemiologic studies of human populations exposed to EtO have been less definitive. In two out of four studies conducted an excess of leukemia was reported. An excess of cardiovascular disease and stomach cancer were reported in one study. All human studies done so far are flawed by small sample size and mixed exposures, problems which we hope to overcome in our study.

The plants in our cohort use or have used EtO in industrial sterilization. Most of the plants sterilize medical products, although a few use EtO to test and repair sterilizers or to sterilize spices. We believe this cohort is the best available for a mortality study of EtO exposed workers; it is the largest such cohort in the smallest number of plants, and it includes workers exposed primarily to EtO alone.

We have conducted an assessment to determine the feasibility of doing a retrospective cohort mortality study of workers exposed to ethylene oxide. In the course of this nine month feasibility study, we visited 11 plants and received information on the number of workers exposed to EtO from approximately 75 companies. We identified 42 facilities which, based on preliminary information, appear to be suitable for inclusion in the study. These plants were selected based upon the number of person years they would contribute to the study. Walk through surveys of these facilities need to be conducted in order to determine the suitability of the facilities for inclusion in the study. To date, walk through surveys have been conducted at 25 of the 42 facilities.

Based on the feasibility assessment, it was estimated that combined, these facilities would contribute 5,621 EtO exposed workers and about 116,000 person years to the study. Based on that estimate, this study would have sufficient statistical power (80%, alpha=.05) to detect a relative risk of 2.7 for leukemia. These estimates, however, were primarily based on correspondence received from the companies involved. Personnel records for 11 of these plants have been copied, and these plants alone will contribute approximately 12,000 workers and 140,000 person years to the study. Thus, our original estimate of 116,000 person years for all 42 sites was a gross underestimate. We are now hoping to be able to establish a cohort which would contribute 270,000 person years to the study which would provide sufficient statistical power (80%, alpha=.05) to detect a relative risk of 2 for leukemia, which is an important improvement in the power of this study. We anticipate that this will require inclusion of an additional 11 facilities to the study.

This study is a retrospective and a prospective cohort mortality study. The results will be analyzed using a modified life table program developed by NIOSH. A synthetic case control study will also be performed for any cancer site found to be in excess in the cohort study. This analysis will include information on cigarette consumption if the observed excess could be explained by these habits.

In the initial phase, the cohort will consist of workers who were exposed to EtO for at least three months prior to 1978. In the future, we plan to extend the followup of this cohort and include workers who were exposed to EtO after 1978.

This study also includes an extensive industrial hygiene component. An exposure characterization is being conducted at each facility using existing environmental monitoring data, and when necessary, collecting new data. Using this information, it will be possible to examine the mortality findings in terms of exposure levels.

Leslie Stayner and Kyle Steenland are the NIOSH project officers, and Richard Hayes is the NCI project officer.

CONCEPT REVIEW FIGURES ARE ESTIMATES ONLY; RFPs, RFAs NOT YET AVAILABLE

The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

RFA 86-CA-01
Title: Cancer control technical development in health agencies
Application receipt date: Jan. 15, 1986

NCI's Div. of Cancer Prevention & Control invites grant applications to enhance the technical capabilities of health agencies in cancer prevention and control.

The goal of this RFA is to enable health agencies at state or selected local levels to enhance their capacity to plan, implement and evaluate cancer control programs. NCI support will provide for access to technical expertise in needs assessment, prioritization, program planning and evaluation. Health agencies are expected to provide for funding of any implementation and operation of resulting cancer control programs.

Applicants must be a state, territorial or local public health department or other agency designated by, operated by or under contract with a state, territorial or local government, with primary cancer control responsibility for a population of at least 500,000. An applicant other than a health department must demonstrate direct involvement of a health department in the application. Applications that include more than one jurisdiction to meet minimum population requirements will be accepted.

Awards will be made as grants. Funding is limited to a maximum of five years. Between five and 10 awards are anticipated depending on the availability of quality applications and funding.

Copies of the complete RFA and additional information may be obtained from Dr. Lawrence Bergner, Program Director, Cancer Control Applications Branch, DCPC, NCI, Blair Bldg Rm 4A01, Bethesda, Md. 20892, phone 301-427-8597.

PROGRAM ANNOUNCEMENT
Title: Combined in vivo application of multinuclear magnetic resonance imaging and spectroscopy
Application receipt dates: Feb. 1, June 1, Oct. 1

The Radiation Research Program of NCI's Div. of Cancer Treatment supports a variety of research programs in the area of medical imaging for the diagnosis and treatment of cancer. This program announcement is to encourage the submission of scientifically meritorious grant applications in the specific area of magnetic resonance. RRP anticipates that the described research can be completed in a period of three to four years and depending on the nature of the awarded projects, renewal applications may be considered.

The pressing need for accurate noninvasive cancer diagnosis mandated this initiative. This announcement emphasizes the continuing interest of NCI in innovative research in magnetic resonance imaging (MRI) and encourages the submission of applications leading to the advancement and improvement of the state of the art in this important area of cancer diagnosis and tumor monitoring.

The major thrust in MRI has been in the direction of visualizing the resonating hydrogen nucleus (proton imaging), there being an abundant supply of hydrogen in the body, chiefly in water, but also in various tissues. The intrinsic differences in proton relaxation times between fluid, fat, muscle, blood, tumor and bone are major determinants of the contrast available for use in proton imaging.

Recent research in MRI shows that nuclei other than hydrogen have been visualized by using higher magnetic field strength plus receiver coils tuned for the specific Larmor frequency. For example, visualization of sodium nuclei, which appear to be in greater concentration in gliomas than in surrounding brain, has been achieved. The phosphorus nucleus has also been visualized, but because of the relatively small amount of phosphorus in tissue, this imaging does not at this time have the clarity of the proton image.

Using magnetic resonance spectroscopy (MRS), murine tumors have been found to exhibit significant change in their in vivo phosphorus spectra at various stages of growth and in response to various forms of therapy. Preliminary experiments suggest that regional changes in blood flow and pH may be documented in localized tumors by combining imaging and spectroscopic methods. Using phosphorus spectroscopy, researchers have been able to differentiate human small cell from nonsmall cell carcinoma of the lung. Other tumors that have been differentiated spectroscopically are human neuroblastoma and breast cancer.

This announcement encourages research with the combined in vivo applications of multinuclear MRI and MRS for increasing sensitivity of tumor demonstration spatially and monitoring of biochemical response to therapy by spectroscopic methodology. Special areas of interest are:

1. Combined in vivo multinuclear research in MR imaging and spectroscopy.

2. Correlation of magnetic resonance images with spectroscopic biochemical analysis in normal and abnormal tissue, that is, following steady state responses to different interventions by following metabolites.

3. Correlation of MRI with biochemical and metabolic changes associated with tumor responses to chemotherapy and radiotherapy; determination of response to and distribution of drugs, and response to radiotherapy by evaluating regional differences in tumor using surface coil spectroscopy and imaging.

4. Evaluation of steady state metabolic changes occurring in specific areas of local tumor masses by spatial demonstration of various parts of the tumor mass (MRI) and by multinuclear studies (MRS) for the measurement of steady state bioenergetics, and glycolytic pathways and by determination of regional blood flow and pH effects.

5. Determination of the clinical applications of the combined biochemical response and imaging correlates of neoplastic tissue.

6. Determination of spectroscopic data by both invasive and noninvasive techniques. Data may be acquired by local surface coil versus shaped, depth correlated RF pulses.

7. Contrast enhancement studies based on multinuclear imaging, paramagnetic contrast agents and chemical shift imaging to localize and

delineate tumor (MRI) and concurrent evaluation of biochemical properties (MRS) in an attempt at tissue characterization.

8. Other areas of pertinent investigation in combined MRI and MRS research inadvertently omitted in this announcement would be appropriate to this program.

The original and six copies of the application (on form PHS-398-Rev 5/82) should be sent to Application Receipt Office, Div. of Research Grants, NIH, Westwood Bldg Rm 240, Bethesda, Md. 20892. For further information, contact Dr. Matti Al-Aish, Diagnostic Imaging Research Branch, RRP, NCI, Landow Bldg Rm 8C-09, Bethesda 20892, phone 301-496-9531.

PROGRAM ANNOUNCEMENT

Title: Studies of dose fractionation and volume late effects in normal tissues using animal models

Application receipt dates: Feb. 1, June 1, Oct. 1

The Radiation Research Program wishes to encourage submission of grant applications for studies of dose fractionation and volume late effects in normal tissues using animal models, especially as they relate to radiotherapy.

Doses used in radiotherapy have become increasingly fractionated. Overall treatment duration was protracted until acute responses, e.g., of skin and mucosae, no longer limited the total dose that could be delivered to a tumor. However, when protraction was sufficient to minimize acute reactions, the total dose became limited by the development of late complications, e.g., dermal contraction, necroses, bone fracture. The change in the type of dose limiting tissue reflects one difference in the fractionation response of early and late responding normal tissues. Whereas repair of sublethal damage occurs in both, regeneration of survival target cells during the course of fractionated radiotherapy is less or absent in the late responding tissues.

There is considerable diversity in the dose fractionation patterns in use in major radiotherapy centers worldwide. Nevertheless, it seems unlikely that valid interinstitution comparisons of therapeutic ratios can be made from the literature.

What is considered to be conventional or standard dose fractionation, consisting of regimens using 1.8-2 Gy/day, 5 days per week, is certainly not the most appropriate for all patients, and may not be the best even for the majority. Experimental evidence, both from the clinic and the laboratory, suggests that better results may be obtained for the same total dose by reducing the dose per fraction and shortening the overall time, and, therefore, the average interval between dose fractions. There is evidence to suggest that reducing the dose per fraction leads to an increase in the tolerance dose for late responding normal tissues which is greater than the increase in dose needed for certain probability of tumor control. Shortening the overall treatment time reduces the extent of repopulation by tumor clonogens, although at the risk of compromising reoxygenation.

A second factor believed to modify the response of normal tissues is the volume of tissue irradiated. The volume effect is frequently discussed but rarely written about. It is a generally agreed upon clinical impression that the phenomenon is important in dermal and spinal cord irradiation and is important where the functional integrity of a complete organ is put at risk.

Although the severity of a normal tissue response increases with increase in the volume or area of tissue irradiated, it is not known if this applies to all tissues, nor whether it varies with fractionation pattern. The volume effect has rarely been well quantified and has not been investigated extensively in experimental animals.

The mechanism involved in the change in effect per unit of dose with change in volume is not understood. It is not known whether it is an increased induction of injury per unit of dose with increase in volume or a decreased ability of the host to recover from or compensate for an equal injury per unit of dose. It is important to understand the volume effect because of the clinical dilemma posed by the tolerance of normal tissues being modified to a significant but poorly quantified extent by the volume irradiated, while in general, larger tumors require larger doses and larger treatment volumes for their control.

In light of these considerations, the RRP encourages investigator initiated grant applications:

1. To determine appropriate animal models for a variety of human tissues which are dose limiting for curative radiotherapy.

2. To select endpoints and evaluation criteria and develop statistical considerations for dose fractionation and volume effects studies.

3. To determine the dose response relationships for late effects for fractionation schemes relevant to radiotherapy.

4. To determine whole and partial organ dose response relationships for late effects for fractionation schemes relevant to radiotherapy.

5. To identify methods for predicting and/or measuring the onset and rate of regeneration in irradiated normal tissues as a function of various dose fractionation patterns.

This list is not meant to be exhaustive. Other applications consistent with the spirit of this announcement are welcome.

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