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BUREAU OF RADIOLOGICAL HEALTH
RESEARCH GRANTS PROGRAM
FISCAL YEAR 1972



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Public Health Service
FOOD AND DRUG ADMINISTRATION

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- FDA 72-8031 Switch Failure Monitoring Device.
- FDA 72-8032 CSU-PHS Collaborative Radiological Health Laboratory Annual Report 1971 (GPO 1712-0160, \$1.25), (PB 211 898, mf only).
- FDA 73-8002 State Radiation Control Legislation, 1971 (PB 212 424, \$3.00).



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BUREAU OF RADIOLOGICAL HEALTH RESEARCH GRANTS PROGRAM FISCAL YEAR 1972

Edited by

Elisabeth H. Boeker

Thelma J. O'Connell

May 1973



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Public Health Service
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Bureau of Radiological Health
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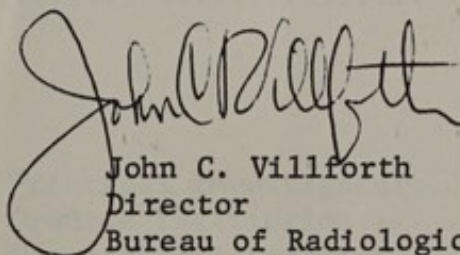
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FOREWORD

The research grant activities described in this publication are funded by the Bureau of Radiological Health, Food and Drug Administration, and administered by the Bureau's Program Office. The aim of research grants is to support the Bureau's efforts to promote the health of man by reducing the hazards from radiation, both ionizing and nonionizing.

To accomplish its basic mission of conducting an electronic product radiation control program, the Bureau develops criteria and recommends standards for safe limits of radiation exposure, develops methods and techniques for controlling radiation exposure, plans and conducts research to determine the health effects of radiation exposure, and provides technical assistance and training to agencies concerned with radiological health problems.

Research activities of both public and private non-profit organizations, research foundations, hospitals and universities contribute substantially to the overall goal of reducing radiation exposure. It is through the grants mechanism that the Bureau utilizes scientific expertise available throughout the Nation to extend and fulfill its mission in radiological health.



John C. Villforth
Director
Bureau of Radiological Health

ACKNOWLEDGEMENT

The Bureau of Radiological Health acknowledges the contribution made by the principal investigators of the respective research grants in supplying information about their research projects; by the grants management staff of the Program Office in selecting and assembling grant information; and the secretarial and editorial staff of the Office of Information for assistance in providing the editing and typing capability and in preparing the material for printing.

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INTRODUCTION

This publication includes descriptions and accomplishments of research projects supported by grants from the Bureau of Radiological Health from July 1, 1969 to June 30, 1972. Information about individual projects was obtained from summary statements prepared by the principal investigators to define their objectives and describe significant results. Project publications which could be identified as grant supported were listed for the duration of the grant.

The first section is comprised of 32 research projects active during FY 1972 and 8 which were terminated. Those grants terminated during FY 1971 or transferred to the Environmental Protection Agency are described in the next section, and those terminated during FY 1970 appear in the final section. Project terminations for FY 1970 and 1971 were included in this publication to provide an accounting of all radiological health research grants since the last publication in FY 1969 by the no longer existing Environmental Control Administration.

Research grants are listed by title, grant number, principal investigator, and institution. The grant number identifies the grant and consists of the two initials RL followed by five digits, a dash and two additional digits. The initials RL designate the Bureau of Radiological Health. The five digits (including zeros) are a sequence identification number, and the two digits after the dash indicate the number of years a particular grant received support. Most of the grants prior to FY 1972 appear with the initials EC which refer to the earlier Environmental Control Administration.

The index at the back of the publication includes alphabetical listings of principal investigators, grantee institutions, and geographical locations, a grouping of grants by DHEW regions and information about the ten regional offices.

THE HISTORY

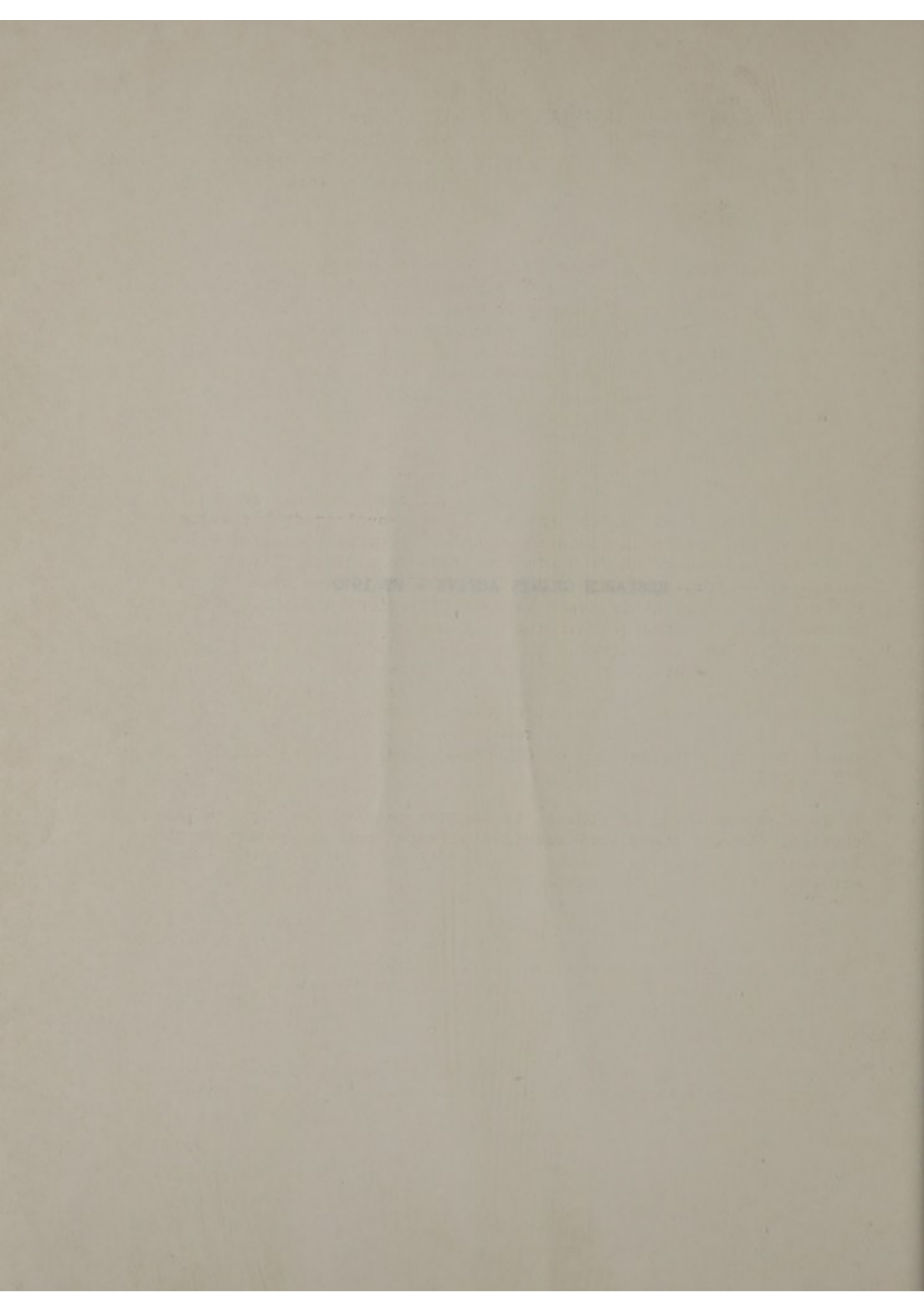
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RESEARCH GRANTS ACTIVE - FY 1972



TRANSFER MECHANISMS IN IRRADIATED
BIOLOGICAL SYSTEMS

Harold C. Box

Health Research, Incorporated
New York State Department of Health
Albany, New York

RL 00009-07

Project Description and Objectives: This project is aimed at achieving an understanding of the molecular changes induced in biological systems by ionizing radiation. Fundamental processes initiated by ionizing radiation, such as oxidation and reduction, dissociation, hydrogen abstraction, etc., can be followed in irradiated biomolecules using specially designed magnetic resonance equipment. Working at liquid helium temperature (4.2°K) the investigators expect to identify the oxidation and reduction products produced by x-irradiation in a variety of amino acids, peptides and nucleotides, and eventually in protein and nucleic acids also.

Significant Results: The most significant progress has been in the continued development of the ENDOR (electron-nuclear double resonance) technique for analyzing radiation damage. Typically several different oxidation and reduction products are produced and stabilized in biomolecules x-irradiated at 4.2°K. The ENDOR technique makes it possible to sort out and identify these various radiation products. A specific example will illustrate the point. If the peptide acetylglycine ($\text{CH}_3\text{CONHCH}_2\text{COOH}$) is subjected to ionizing radiation at 4.2°K several paramagnetic species are formed whose absorptions overlap so that analysis by conventional ESR (electron spin resonance) spectroscopy is hopeless. Using ENDOR, however, it can be rigorously demonstrated that the radiation damaged products consists of three reduced species ($\text{CH}_3\text{CO}^-\text{NHCH}_2\text{COOH}$ and two different conformations of $\text{CH}_3\text{CONHCH}_2\text{COOH}$) and one oxidation product ($\text{CH}_3\text{CONHCH}_2$).

It is also possible, of course, to monitor many of the physical and chemical changes these very reactive primary species undergo as the temperature is allowed to rise. Again ENDOR is extremely useful in studying these secondary processes.

Relatively few low temperature ENDOR studies of radiation damage have been completed to date but it is clear that the technique can provide detailed information concerning radiation damage at the molecular level. And molecular damage must underlie the biological manifestations of radiation (carcinogenic, therapeutic and genetic) observed at the level of the organism.

The capability of producing, stabilizing and analyzing molecules in their oxidized and reduced states has implications in other fields of

science. In chemistry, for example, ENDOR analysis can provide detailed information about the distribution of the unpaired electron in oxidized and reduced molecules. These data are ideal for checking theoretical calculations of the electronic wavefunction obtained from quantum mechanical considerations.

Publications:

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RADIATION DOSE AND DIAGNOSTIC
ISOTOPE PROCEDURES

Edward M. Smith
Society of Nuclear Medicine
New York, New York

RL-00029-06

Project Description and Objectives: The primary objective of the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine is to provide the best possible estimate of the absorbed dose to patients resulting from the diagnostic or therapeutic use of internally administered radiopharmaceuticals. In order to achieve this objective the Committee collects, analyzes, and publishes in convenient form necessary data on the distribution of radiopharmaceuticals; physical and nuclear decay scheme data for relevant radionuclides; and physical, chemical, and biochemical properties which may effect the biological behavior of radiopharmaceuticals. The work of the MIRD Committee is expected to continue as long as new diagnostic and therapeutic radiopharmaceuticals are being developed.

Significant Results: The results of the MIRD Committee are published as supplements to the Journal of Nuclear Medicine and as Dose Estimate Reports incorporated into the Journal of Nuclear Medicine. The Committee will publish its first Dose Estimate Report in January, 1973 which will summarize the dose resulting from the intravenous administration of selenium-75 as selenomethionine. There are 19 other radiopharmaceuticals that the Committee is currently working on and will eventually be published as Dose Estimate Reports.

Publications:

SUPPLEMENT NUMBER 1 (1968)

- Pamphlet #1 A schema for absorbed-dose calculations for biologically distributed radionuclides.
- Pamphlet #2 Energy deposition in water by photons from point isotropic sources
- Pamphlet #3 Absorbed fractions for photon dosimetry.

SUPPLEMENT NUMBER 2 (1969)

- Pamphlet #4 Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation.

SUPPLEMENT NUMBER 3 (1969)

- Pamphlet #5 Estimates of absorbed fractions for monenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom.

SUPPLEMENT NUMBER 4 (1970)

- Pamphlet #6 Radionuclide decay schemes and nuclear parameters for the use in radiation-dose estimation, Part 2.

SUPPLEMENT NUMBER 5 (1971)

- Pamphlet #7 Distribution of absorbed dose around point sources of electrons and beta particles in water and other media.
- Pamphlet #8 Absorbed fractions for small volumes containing photon emitting radioactivity.

SUPPLEMENT NUMBER 6 (1972)

- Pamphlet #9 Radiation dose to humans from $^{75}\text{S}_e$ -L-Selenomethionine.

STUDIES OF RADIATION DAMAGE TO
BIOLOGICAL MATERIALS

Roy S. Anderson
Clark University
Worcester, Massachusetts

RL 0065-10

Project Description and Objectives: The goal of this research is to discover the effect of high energy radiation in damaging molecules of biological interest. Radiation damage occurs by breaking a chemical bond, with an atom or group of atoms being removed. Such alterations of molecules render them weakly magnetic; the highly sensitive method of electron spin resonance spectroscopy may then be utilized. These studies must be conducted using single crystals, so that the exact nature and location of the damage may be understood. Crystals are exposed to x-rays or gamma-rays. Resulting damage is frequently stably trapped in the crystalline lattice for periods of days to years.

Significant Results: Experimental results indicate that in saturated molecules radiation damage is principally in the form of abstraction, that is, the loss of an atom by the breaking of a chemical bond. There also appears to be an ordering of the radiation sensitivity of the various chemical bonds: carbon-sulphur bonds appear to be the most susceptible to radiation, followed by carbon-nitrogen bonds, carbon-hydrogen bonds, and carbon-oxygen single bonds, in descending order.

Of the various radiations used, gamma-rays and x-rays are highly effective in producing damage. Ultraviolet rays are ineffective in damaging molecules in crystals. Of the various particles investigated, neither thermal neutrons nor thermal hydrogen atoms were found capable of creating significant radiation damage.

In the case of unsaturated covalent compounds, radiation damage appears to occur by addition, that is, by having atoms (or groups of atoms) attach themselves directly to the molecule at the double or triple bond. In this case, the attaching atoms are believed to originate in waters of crystallization that are first damaged by the radiation.

Publications: Fujimoto, Minoru, "Electron Spin Resonance of a Radical in Irradiated Single Crystals of Itaconic Acid," J. Chem. Phys., 39:846-847 (1963).

Rao, M. J. and R. S. Anderson, "Electron Spin Resonance in Gamma-Irradiated Single Crystals of Hydroxylated Organic Compounds," J. Chem. Phys., 42:2899-2904 (1965).

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- DuVarney, R. C. and R. S. Anderson, "An Analog Computer for the Rapid Analysis of Electron Spin Resonance Spectra," J. Magnetic Resonance, 3:235-239 (1970).

RBE OF MONOENERGETIC NEUTRONS

Harald H. Rossi
Columbia University
New York, New York

RL 00074-11

Project Description and Objectives: The relative biological effectiveness (RBE) of neutrons is being investigated as a function of their energy. The neutron source is a 5 MeV Van de Graaf accelerator which is probably the largest facility entirely devoted to radiobiology and radiation protection. It produces six beams of neutrons and charged particles and occupies about half the space of the former cosmotron accelerator. A great variety of organisms and effects are under examination. The principal interest is in higher organisms particularly mammals.

Significant Results: Previous findings under this grant have indicated that although neutron RBE depends on the effect under consideration, its dependence on both neutron energy and magnitude of the dose is virtually the same for all effects that have been studied. Except for one recently discovered exception, the RBE of neutrons relative to x and gamma radiation has been found to increase with decreasing absorbed dose, reaching levels which are much higher than those previously found. This has obvious implications to radiation protection because it indicates the need for an increase in QF of high LET radiation. On the other hand it also indicates that risk estimates for x and gamma rays (the most commonly encountered radiations) may be unduly high if based on linear extrapolations. During the last year the results of the research previously carried out permitted the formulation of the theory of dual radiation action according to which the effects of all radiations on higher organisms can be interpreted in terms of energy deposition in small regions within the cell. The cardinal finding is that the biological effect is proportional to the square of the energy concentration. It is believed that further development of this theory will not only be of theoretical significance but will also be of practical import to both radiation protection and radiation theory.

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NEOPLASMS IN IRRADIATED HUMAN
POPULATIONS

Louis H. Hempelmann
University of Rochester School
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Rochester, New York

RL 00078-09

Project Descriptions and Objectives: To investigate induction of cancer and benign tumors in man by radiation exposure in a continuing study of 4,872 persons. Most of these people have a history of receiving radiation therapy in childhood for alleged thymic enlargement or for lymphoid hyperplasia of the nasopharynx. In addition, there is a series of women given x-ray treatments for acute post-partum mastitis. As controls, 7,752 non-irradiated siblings of the irradiated subjects will be used. In particular, the mechanisms by which the irradiation of the thyroid induces cancer will be studied and the best means of treating and/or preventing this disease will be explored.

Significant Results: In the past ten years, significant progress has been made in quantitating the risks of developing thyroid and other neoplasms (benign as well as malignant) after radiation exposure in childhood. The best risk estimate of such exposure is 9.3 cases of cancer per year per million children exposed to an average of one rad each. Also, the mechanism(s) by which radiation induces thyroid neoplasms and the pathogenesis of radiation-induced thyroid cancer in man have been worked out. Furthermore, a considerable clinical experience has been gained in the treatment of radiation induced thyroid neoplasms in young or middle-aged patients. In addition to these epidemiological studies of persons irradiated in childhood, a pilot study of women given x-ray treatments for acute post-partum mastitis revealed an apparent excess of benign and malignant breast tumors.

In the past 18 years, there have been three mail surveys of almost 3,000 young adults treated with x-rays in infancy for thymic enlargement. A fourth survey has been completed and the data are being analyzed. Preliminary study indicates that thyroid neoplasms continue to develop as the subjects enter the third and fourth decade of life. Three new thyroid cancers and several other forms of radiation-induced neoplasms have occurred in subjects in their thirties. A distinct dose response can be seen when the incidence of thyroid cancer and of pooled extrathyroid tumors are plotted against dose. An apparent excess of rare diseases, some of which have auto-immune "overtones" (including one case of myasthenia gravis), has prompted the investigators to undertake a thorough evaluation of the immunological status of selected patients in the treated series.

Recently, a study of radiation-induced chromosome aberrations in the thyroid cells of some of the irradiated patients with neoplasms has been published. In patients who were irradiated in infancy and who developed tumors 29-37 years later, approximately one-third of the cultured thyroid cells contained abnormal chromosomes. This is in contrast to other patients without a history of radiation exposure but with thyroid tumors who were given tracer doses of I^{131} preoperatively. The thyroid cells of these patients showed no excess of chromosomal abnormalities. The latter study has clear implications for the public health aspects of radioactive fallout in that radiation delivered at a low dose rate such as would occur after world-wide fallout seems to be less effective in producing chromosome damage than irradiation at a high dose rate as in x-ray therapy.

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FOLLOW-UP STUDY OF IRRADIATED
TINEA CAPITIS CASES

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RL 00085-08

Project Descriptions and Objectives: The purpose of the study is to characterize the nature and magnitude of long-term radiation injury due to X-ray epilation of the scalp. The study population consisted of about 4,200 cases treated for tinea capitis (ringworm of the scalp) of which 2,400 cases received X-ray epilation. The radiated and control groups were well matched on socioeconomic status of parents, age, age at Tinea treatment, race and sex. Doses to the structures of the head were appreciable: 450-850 rad to the scalp, up to 400 rad to the cranial marrow, and 70-175 rad to the brain.

The entire registry was surveyed between 1962 and 1968, and a second follow-up is about 95 percent completed. The following potential indicators of deleterious effects are being assessed: verified illness experience and mortality; educational and occupational history; penal experience and military disqualification. Medical and psychiatric examination programs and a dosimetric study were also undertaken.

Significant Results: This study provides opportunity to assess the tumorigenic effects of radiation to head structure without appreciable radiation to other body areas, unlike the several well-known studies of whole-body radiation. It also provided an opportunity to examine the possible psychogenic effects of radiation.

The first survey, which assessed patients from 5 to 25 years post-Tinea treatment, demonstrated an incidence of cancer and leukemia 10 times greater in the irradiated cases than in controls and of confirmed mental illness 2.5 times greater.

Total medical confirmation to date has shown differences between the irradiated and control groups in disease frequency for several categories of disease. (Crude incidence rates per thousand are given in parentheses.)

1. Cancer and leukemia

Overall the irradiated group had 25(12.2) cases and the control group 7(5.0) cases. This difference resulted primarily from malignancies of the head and neck, where there were 12(5.9) and 1(0.7) cases respectively; with a morbidity ratio of 8.2. The irradiated head and neck malignancies included 6 basal cell carcinomas and 3 brain tumors. There were also 4(2.0) cases of leukemia in the radiated group and 1(0.7) among the controls.

2. Benign tumors

Fifty-three(25.9) cases with benign tumors of the head and neck were diagnosed in the irradiated group versus 14(10.0) in the controls, but no differential was found in tumors of other parts of the body (17.6 vs. 19.4 per thousand). Six(2.9) thyroid adenomas were diagnosed in the radiated group and one(0.7) in the controls.

3. Psychiatric illness

Diagnosed psychiatric illness was 40 percent higher in the irradiated group with 161(78.8) cases vs. 72(55.2) cases among controls. A psychiatric examination program also confirmed by both psychiatric interview and psychologic testing that there were small, though significant, differences between the groups in mental disorders.

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RADIATION PROTECTION AND
MEASUREMENT

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RL 00096-07

Project Description and Objectives: To collect analyze and disseminate information and recommendations for radiation protection and measurement; and to stimulate the exchange of ideas in radiation problem areas.

The Council formulates recommendations on radiation protection and measurements which represent the leading scientific thinking on these questions and are of substantial benefit to those utilizing radiation producing equipment or materials.

Significant Results: Principal activity centered around the following areas each with its own scientific committee: Basic Radiation Protection Criteria, Heavy Particles (Neutrons, Protons, and Heavier), Monitoring Methods and Instruments, Medical X and Gamma Ray Protection Up to 10 MeV (Structural Shielding Design), Safe Handling of Bodies Containing Radioactive Isotopes, X-Ray Protection in Dental Offices, Veterinary X-Ray Protection, High Energy X-Ray Dosimetry, Specification of Radium Substitutes, Brachytherapy and Administered Radioactivity.

Scientific Committee 1 was engaged in the drafting of NCRP Report No. 39, Basic Radiation Protection Criteria. The work on the report was completed in 1970 and the report was published in January 1971. The report has already received very wide distribution and it appears to meet a vital need.

Scientific Committee 4 completed in 1970 its work on a report to supersede NCRP Report No. 20, Protection Against Neutron Radiation Up to 30 Million Electron Volts. The new report NCRP Report No. 38, Protection Against Neutron Radiation, was published in January 1971.

Significant progress was made on the revision of the draft report on monitoring methods and instruments on the basis of comments resulting from the Council review of the draft prepared by Scientific Committee 7. Portions of the report have now been rewritten on the basis of the Council members comments and the rewriting of additional subsections is now underway. It is expected that this work can be completed in the near future. It is not yet clear whether the revised report will have to be resubmitted to the Council members for additional review.

Scientific Committee 9 moved into inactive status in 1970 following the completion of its work on NCRP Report No. 34, Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV-Structural Shielding Design and Evaluation. The report was published in March 1970.

Scientific Committee 13 on Safe Handling of Bodies Containing Radioactive Isotopes completed its work on a report which sets out the Council's recommendations relating to precautions in the management of patients who have received therapeutic amounts of radionuclides. The report also brings up to date the NCRP recommendations on the safe handling of bodies containing radioactive materials. NCRP Report No. 37, Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides was published in October 1970.

With the publication of NCRP Report No. 35, Dental X-ray Protection, Scientific Committee 16 completed its work. The report was published in March 1970.

Early in 1970, Scientific Committee 17 on Veterinary X-Ray Protection completed the final revision of a new report, Radiation Protection in Veterinary Medicine. The report was published as NCRP Report No. 36 in August 1970.

Scientific Committee 26 on High Energy X-Ray Dosimetry is engaged in the development of NCRP recommendations directed particularly to the problems of calibration and measurement for high energy x-ray sources used in therapy. The initial draft of the NCRP report being prepared by the Committee is approximately two thirds complete. It is not yet possible to predict when the committee will complete the drafting work and submit the report to the Council members for review.

Scientific Committee 27 on Specification of Radium Substitutes completed the second draft of the brief report being developed by the Scientific Committee. It is expected that the Committee's draft will be ready for submission to the Council members in the near future.

The report drafted by Scientific Committee 29 on Brachytherapy was completed late in 1971 and published in March 1972 as NCRP Report No. 40, Protection Against Radiation from Brachytherapy Sources.

Following the reorganization of the Council's activities relating to internal emitters in 1969, several new Scientific Committees were constituted. Scientific Committee 32 on Administered Radioactivity is one of these. The Committee has drawn plans to devote its attention to an examination of the criteria for selecting a radionuclide for a particular use. Much preliminary work remains to be done, but the Committee has utilized the computation facilities made available to it to complete certain calculations on a typical radionuclide. This "test run" proved the feasibility of the type of approach the Committee believes may be appropriate.

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RADIATION CHEMICAL STUDIES
ON HEMOCYANINS

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RL 00098-07

Project Description and Objectives: The ability of irradiation to kill cancer cells and to modify cellular processes is related to the levels of oxygen present. Oxygen from the air becomes available to animals through oxygen-carrying proteins such as hemoglobin in man and hemocyanin which is present in the blood of many shell fish. Hemoglobin picks up oxygen from the blood through iron atoms which form an integral part of the protein structure while hemocyanin uses copper instead of iron for oxygen-carrying. In both cases, atomic radiation interferes with the ability of these proteins to pick up oxygen. The objectives of this project are to clarify the mechanisms by which relatively small doses of radiation modify the functioning of oxygen-carrying proteins and to determine the nature of the active site, i.e., what structural and chemical properties associated with the protein-bound copper enable the oxygen-carrying protein to function. This work is important for an understanding of the mechanisms of radiation injury and repair phenomena as well as energy-transfer mechanisms.

The methods employed in these studies include the use of gamma radiation from a cobalt-60 source. Oxygen-carrying in hemocyanins is measured spectrophotometrically. Removal of oxygen from hemocyanin is carried out by bubbling oxygen-free helium through the solution. Selective removal of free radicals produced by irradiation is accomplished by means of scavenging agents. Thus, sodium formate removes the oxidizing OH radical while sodium chloroacetate removes the reducing hydrated electron. The techniques of circular dichroism and NMR line broadening are employed to learn more about the active site itself, i.e., the site in the protein containing the oxygen binding copper.

Significant Results: In studies with solutions of hemocyanin it has been shown that the ability of hemocyanin to carry oxygen depends on the apparent oxidation state of the copper. When the protein-bound copper is in a lower oxidation state, the +1 cuprous form, the hemocyanin picks up oxygen. However, when the copper is promoted to a higher oxidation state, the +2 or cupric form, before combination with oxygen, hemocyanin does not pick up oxygen. It turns out that irradiation transforms cuprous copper to the non-oxygen carrying cupric state by producing oxidizing substances, either hydrogen peroxide when the oxygen is present, or the oxidizing hydroxyl free radical, which is formed even with oxygen is not present. Consequently by removing hydrogen peroxide or the OH radical, it is possible to prevent the loss of oxygen-carrying by hemocyanin during or after irradiation.

It is possible to restore the oxygen-carrying ability of radiation or chemically inactivated hemocyanin by giving the protein more irradiation. This seemingly strange result arises from the fact that irradiation in the presence of an OH scavenger permits the reducing hydrated electron to reduce protein-bound cupric copper to the cuprous state without competition from the oxidizing OH radical. It is also possible to enhance the radiation damage by removing the reducing radical, e.g., with chloroacetate, during irradiation.

Of fundamental interest is the fact that in the case of hemocyanin (*Limulus*) obtained from one species of marine life, the horseshoe crab, irradiation does not restore the oxygen-carrying ability even though the copper of the inactivated protein is reduced back to the cuprous form. A variety of techniques has been applied in order to learn why horseshoe crab hemocyanin is so different from other hemocyanins. It is found, for *Limulus*, for example, that its circular dichroism spectra, which provide information about the internal environment of the active copper sites, is uniquely different from other hemocyanins. It is postulated that the oxygen in *Limulus* is bound to the copper at the active sites in a different manner from that in other hemocyanins. More specifically, in the usual hemocyanin the oxygen molecule is held between two copper atoms while in *Limulus* the experimental observations are more consistent with a model in which the oxygen molecule is bound to one copper atom, which in turn is bound to another copper atom by a sulfur bridge.

Finally, the results of the techniques known as NMR line-broadening has provided direct evidence for the presence of paramagnetic copper, essentially "cupric" copper, in oxyhemocyanin. In addition, it is found that the copper in oxyhemocyanin has two open positions available for binding of small molecules. Such information is needed to solve the problem of how an oxygen-carrying protein functions--a question fundamental to the general problem of how a cell functions.

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ABSORBED DOSE DUE TO INTERNAL
RADIATION EMITTERS

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RL 00114-03

Project Description and Objectives: This project is an investigation of advanced methods of dose calculation for the estimation of radiation dose resulting from internally administered radioisotopes in nuclear medicine. The gamma ray dose calculations are based principally on Monte Carlo methods of gamma ray diffusion. Experimental observations are designed to corroborate the results of the Monte Carlo calculations.

The rapid growth of nuclear medicine and the extension of techniques to the diagnosis of disorders of nearly every body organ has resulted in increased concern for precise estimation of radiation dose. Levels of activity are increasing due to the desire to obtain more statistically significant data to improve the diagnostic ability of these tests, and tests which were done on a research basis several years ago are now being performed wide scale on large numbers of patients. All of these reasons have dictated towards improved dosimetry techniques.

The methods that have been developed in this study and the data that has been generated have significantly altered the concepts and techniques of gamma ray dosimetry of internal emitters. The investigators have developed the concept of absorbed fraction and have, with others, generated large amounts of data to be used in practical clinical problems. The results of our efforts are strongly reflected in the publications of the MIRD Committee of the Society of Nuclear Medicine.

Significant Results: Their previous calculations of absorbed fraction in ellipsoids and cylinders have been extended to include small volumes and lower energies. They are currently working on the important problem of calculating dose from one organ to another using a procedure that they feel will be effective in a large range of clinical situations.

Their studies on the experimental verification of absorbed fraction are continuing and they believe that this data will provide very useful confirmation of the theoretical calculations. This confirmation has long been needed and desired.

The use of absorbed fractions, based on their prior work in this field, is becoming widespread for gamma ray calculations. They have essentially supplanted the previous techniques for such dose estimation. Forthcoming data on specific absorbed fraction and absorbed fractions from organ to organ will fill an equally important role in the calculation of radiation dose in nuclear medicine.

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NEURAL DETECTION OF IONIZING RADIATIONS

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RL 00119-05

Project Description and Objectives: Man and laboratory animals can detect very small amounts of ionizing radiations under certain circumstances. Available evidence suggests that detection occurs as a result of neural receptor stimulation. The objective of this investigation is to examine the problem of biodetection in primitive species with less differentiated nervous systems so as to provide information that is instructive in the interpretation of this phenomenon in man and other mammals. Both behavioral and electrophysiological techniques are employed to identify prompt responses to brief exposures and in the analysis of systems that serve usefully as biodetectors for the presence of ionizing radiations.

Significant Results: It has been found that the ability to detect the occurrence of brief bursts of x-rays is a more common phenomenon than has been suspected previously. A broad spectrum of organisms have been observed to react promptly to a brief burst of x-rays. A primitive coelenterate (the sea anemone), possessing only an aganglionic nerve net and no organized sense organs, can detect a one second burst at 20 R/second. Several observations of this type indicate that a complex nervous system and highly specialized receptor organs are not essential for detection. In the first observation of its kind, the coelenterate was found to respond to the lower photon energies of the ultraviolet range as well as to energetic x-ray photons. This opens up the possibility that the x-ray energy transferred by excitation may stimulate photoreceptor systems and lead to radiation detection. The efficiency of radiation detection appears to improve with an increase in the differentiation of nervous system and specialization of receptor systems. For example, while 20 R elicits a response in the simple coelenterate, echinoderms, with moderately complex neural development, can detect an exposure to 5 R. Insects with highly developed sense organs (e.g. carpenter ants) will react to less than 1 R. Several systems have been found that are available routes for radiation detection in the lower forms. Based on electrophysiologic measurements, the dark-adapted eye of a crustacean has proven to be an especially sensitive detector of ionizing radiations. Electroretinographic responses to soft x-rays (70 kVp) occurred at the 35-40 mrad level, and responses to energetic beta radiations (2.26 MeV max.) occurred with only 1-2 mrad. Among the other highly sensitive detection systems are the antennae of insects. Ants respond immediately on x-ray exposure above a rate of 100 mR/sec. The principle detection pathway has been found to be the olfactory sensilla, with radiation acting in or on the surface of these

receptors. There remains in insects, yet other pathways for detection, since removal of visual and olfactory pathways does not eliminate immediate responses to high rates of exposure. Detection of radiation has been observed clinically in patients under particular circumstances. Recently, astronauts have reported on visual reactions that appear to be elicited by cosmic radiations during lunar flights. Detection appears to be widespread in the animal kingdom and involves several sensory mechanisms. As yet, they have insufficient information on which to assess its significance in radiological health.

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REMOVAL OF AM-241 FROM HUMANS
WITH DTPA

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RL 00122-04

Project Description and Objectives: The objectives of this project are to increase the rate of elimination of Am-241 from several humans who were accidentally exposed, and to develop a quantitative description of the removal of Am-241 from humans under treatment with the chelating agent, DTPA. These human cases provide unique opportunities for the *in vivo* measurements of Am-241 in various body compartments, and in excreta, as a function of time. The specific aims of this project area: (1) to obtain additional measurements of the body distribution, translocation, and retention patterns of Am-241 in human cases currently under DTPA treatment; (2) to assess the effectiveness of long-term DTPA treatment as well as any potential adverse effect; (3) to improve techniques for the quantitative measurements by whole-body counting and chemical analysis, and (4) to develop new and improved therapy for Americium and other toxic radioisotopes by employing a mixture of chelating agents, i.e., use of mixed ligand complexes. Data on the retention, translocation and elimination of Am-241 in humans under DTPA treatment are obtained from whole-body counting. Excretion of Am-241 in urines are analyzed by a radiochemical method including: wet ashing, separation of Am-241, electrodeposition of Am-241, and α -counting.

Significant Results: An individual who had for several years annealed and compressed compacts containing Americium oxides was whole-body counted in May 1967 and found to have a body burden of 1.8 nCi (about 2×10^{-7} of the total quantity processed). Infusions of 1 g DTPA in 250 ml saline were administered weekly from September 1967 to December 1968. After 18 days without treatment, 0.5 g DTPA were given, by intravenous injection, twice weekly from January to April 1969, followed by a single 1 g DTPA treatment per week. *In vivo* wholebody counting data and excretion analyses by radiochemical method, as well as gamma counting of bulk urine samples, show that: 1 g DTPA per week continues to be effective (by at least a factor of five) in increasing excretion rates of systemic Am-241. It is found that treatment with 1 g DTPA per week removes Am-241 at a rate of 5.5 nCi per week. This removal rate was the same for two 0.5 g DTPA treatments per week as for a single 1 g DTPA treatment per week. Mathematical models are being fitted to the dynamic changes in organ content and excretion rates to obtain a general quantitative formulation of Americium metabolism for use in internal dose estimation and treatment planning. To date, more than half of the initial body burden has been eliminated. So far, no adverse side effects have been noted on this individual.

Urinary excretion of zinc of this same individual with and without DTPA treatment have been studied by analysis with atomic absorption spectrophotometry. It is found that DTPA treatment enhances urinary excretion of zinc by a factor of 20-25. The enhanced zinc excretion is estimated to be about 30-50 percent of normal dietary intake. The patterns of daily urinary zinc excretion, under DTPA treatment, are found to be very similar to that of Am-241.

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STUDIES OF THERMOLUMINESCENT DOSIMETER SYSTEMS

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RL 00125-04

Project Description and Objectives: The objective of this research program is to improve the usefulness of thermoluminescent dosimeter systems in the detection of ionizing radiation and to extend this capability to non-ionizing regions of the electromagnetic spectrum. Current work includes thermoluminescent studies in a number of materials after x-ray and ultraviolet irradiation, in crystals with carefully controlled impurity concentrations and lattice defect structures. The techniques used include thermoluminescence measurements, ionic conduction, nuclear magnetic resonance, ionic thermocurrents, and optical absorption. These studies provide basic scientific knowledge regarding the relation between defect-related properties and thermoluminescent processes while supplying the necessary understanding for the development of improved thermoluminescent radiation dosimeter crystals.

Significant Results: Thermoluminescent radiation dosimetry utilizes the light-emitting properties of solids when heated following irradiation. LiF is highly useful in this regard and is now widely used in radiological health applications. LiF does suffer, however, from variation in sample sensitivity and from a non-linear thermoluminescence vs. dose response.

Current results have shown that thermoluminescent response varies markedly with heating temperature, cooling rate, and atmosphere during annealing treatments. Correlation of the thermoluminescent response with ionic conductivity results has enabled the identification of the lattice defects responsible for the major dosimetry peaks in LiF as impurity-vacancy complexes. This knowledge will aid in the elimination of many of the sensitivity problems encountered in practice.

Current results also show that hydroxide ion impurities decrease the sensitivity of thermoluminescence in LiF. The association of OH-ions to an impurity-vacancy complex changes the thermoluminescent characteristics of the complex, reducing the resultant thermoluminescent output. The presence of a significant concentration of impurity-vacancy-OH ion complexes is also found to eliminate the non-linear thermoluminescence vs. dose response in these crystals. This is highly significant to radiation dosimetry, since a wider range of linear response allows for greater ease in use.

Further studies in other material systems including $\text{Li}_2\text{B}_4\text{O}_7$, MgO , Al_2O_3 and CaF_2 , have also been performed. Studies on a particular type of

Al_2O_3 have shown the property that the peak temperature of the major glow peak is dependent upon the radiation dose. This may be important in future dosimetry development, since a dosimetry system based on peak temperature rather than peak height or integrated thermoluminescent output could be very useful in certain specialized applications. A dosimetry system based on this idea could be used with any material in which a thermoluminescent peak temperature changes with exposure. Such a system would be of greatest use for a material that shows the greatest change in peak temperature with exposure.

Investigations of other dosimetry materials which may be useful in other regions of the electromagnetic spectrum are currently underway. MgO has promise for use as a direct ultraviolet radiation detector, and a survey of other materials is in progress.

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TIME-RADIATION DOSE RELATIONSHIP
TO BIOLOGIC DAMAGE

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Winston-Salem, North Carolina

8 R01 RL 00129-04

Project Description and Objectives: The objective is to determine if the response of biologic systems to radiation is related to the time period over which the radiation dose is delivered. Using mitotic inhibition and production of chromosomal abnormalities in regenerating rat liver as the endpoints for study, they are comparing the effects of x-irradiation delivered immediately to irradiation over longer time periods from clinically important radionuclides of varying half lives. There is a growing tendency to use ever-shorter lived radionuclides in larger amounts in patient diagnosis in nuclear medicine. Potential harmful effects are estimated at present only on the total dose delivered to the patient with no regard to the time interval over which the dose is delivered. This research would help establish if a potentially important time-dose relationship is being overlooked in the wide-spread clinical use of short-lived radionuclides.

Significant Results: Using the capacity of liver cells to divide and the production of chromosomal aberrations (bridges) as endpoints, our results compare the effect of a given dose of radiation when it is delivered at differing dose rates. The irradiation will be given as an essentially instantaneous x-ray dose to the hepatic region of the rat or by radioactive colloids of differing half-lives which are deposited in the liver after intravenous injection.

The initial studies of the effects of x-ray on regenerating rat liver demonstrated a number of concepts necessary to other researchers using this system for radiobiologic experiments. After partial hepatectomy there is great variability in the levels of both DNA synthesis and mitosis. These variations make the demonstrating of the effects of radiation difficult. Mitosis is more radiosensitive than DNA synthesis and is completely inhibited after 500 rads of x-ray during early phases of mitotic activity. A dose of 250 rads did not completely inhibit mitosis. Persistent chromosomal aberrations were produced in consistently large numbers by x-ray (approximately 20 percent of the anaphase and telophase figures demonstrated bridges). Thus, these observations indicate that mitotic inhibition and production of chromosomal aberrations are appropriate endpoints when regenerating liver is used for studies of radiation effects.

Based upon organ distribution studies after the intravenous injection of radioactive Gold-198 and Indium-113m colloids, they were able to calculate the dose to the livers of rats after treatment. They compared

the effectiveness of the same radiation dose delivered in a few minutes with x-ray, over a few hours with Indium-113m, or over 18 days with Au-198. The production of persistent chromosomal aberrations was used as an endpoint and data was obtained from 1000 rads down to 125 rads.

These studies indicate that irradiation with x-rays and Indium-113m is approximately twice as effective as Gold-198 in inducing chromosomal bridges in the dose range studied. The relationship of damage to dose appears to be linear. This provides specific evidence for a time-dose effect in the production of persistent cellular damage, indicating that a potentially important time-dose relationship may exist in the clinical use of radionuclides.

Publications: Pizzarello, D. J. and R. L. Witcofski, "Regenerating rat liver: a good system for radiobiological studies," *Radiology* 100:163-167 (1971).

ALTERATION OF MUTATION RATE IN
MAMMALS

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University of Texas
Houston, Texas

RL 00133-03

Project Description and Objectives: Based on results with lethal mutants induced in *Drosophila*, a large-scale study was carried out to determine whether it is possible in mammals to reduce mutation rate induced by irradiation significantly by materials that are nontoxic, in therapeutic doses. The effect of antibiotics on dominant lethal mutations produced by irradiation in mice and the effect of the gnotobiotic state on mutation rate after irradiation has been carried out in the course of the study.

Significant Results: The administration of Actinomycin D, an inhibitor of RNA synthesis, and Puromycin, an inhibitor of protein synthesis, in dosages that were nontoxic inhibited the number of dominant lethal mutations induced by X-irradiation in mice. More recent experiments have been conducted in which the numbers of mutations induced by irradiation in axenic animals was compared to the number of dominant lethals induced in those exposed to the ambient atmosphere.

Bateman's method for scoring dominant mutations was utilized in this latter study and mutation rates after irradiation were found to be lower in axenic than in conventional groups. Males were divided into five groups: those irradiated and given Actinomycin D two hours before and two hours after irradiation, those treated with X-irradiation and given Puromycin two hours before and two hours after treatment, and those irradiated only. Fourteen days after irradiation the isolator seals were broken and the male mice mated to six conventional females each for five days. Celiotomy was performed on the females and results tabulated 18 days after mating. The difference in numbers of dominant lethal mutations found in those animals given antibiotics was not different in germ free and conventional groups.

Publications: None.

CHEMICAL RADIOPROTECTION
FEASIBILITY STUDY

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Kansas City, Kansas

RL 00405-02

Project Description and Objectives: Chemicals are usually tested for radioprotective ability by measuring 50 percent mortality in 30 days in large groups of animals. This project is designed to determine the feasibility of using the stem cell system in the polycythemic mouse as a test system for radioprotective action. If the model proves feasible, it should be possible to rapidly (five days) assess radioprotective ability of chemicals to sub-lethal doses; in particular, doses which humans can be accidentally or purposefully exposed.

Significant Results: Chemical toxicity data have been obtained for intraperitoneal and intravenous injection of AET, MEA, 5-HT, and WR-2721. Experiments were then performed to determine the optimum time to inject the chemical before irradiation. These chemicals have been tested using both lethality and percent iron incorporation in stem cells as biological end points. The optimum time interval between administration of the radioprotector and irradiation is the same for both stem cell response and lethality; probably reflecting hematopoietic system involvement in mortality at the LD₅₀ level.

Chemical radioprotection has been demonstrated for each agent at doses below 200 rads. This is well below the LD_{50/30} of 700 rads for the MCR/ICR mouse used in these experiments. Radioprotection is also seen in the 50-100 rad range with both AET and WR-2721.

The primary concern for irradiation of human populations is with genetic and hematopoietic effects. The results of this study may be applicable to situations where humans are exposed to significant, but sub-lethal radiation doses.

Publications: None.

Department of Health
University of the Pacific
San Francisco, California

CHEMICAL RADIATION
PROTECTION STUDY

EL 60503-02

Protein metabolism and synthesis. Chemicals are usually tested for
radioactive activity by measuring the amount of radioactivity in the
in large groups of animals. This project is designed to determine the
feasibility of using the same cell system as the previous study
as a test system for radioactive activity. In the present study
feasible, it should be possible to rapidly (two days) screen radio-
protective ability of chemicals in cell-based systems in particular,
those which humans can be acutely exposed to.

Significant results. Chemicals tested have been evaluated for
interference and interference in the cell, DNA, RNA, and protein
synthesis were then measured in the same cell system. The results
the chemical before irradiation. The chemicals have been tested using
both lethality and percent cell survival as end points. The results
and points. The results show that the chemical interference of the
radioactivity and irradiation in the same cell system will be more
and lethality probably reflecting a synergistic effect in
activity of the cell.

Chemical radiation protection has been demonstrated for cells exposed to doses
below 100 rads. This is well below the LD₅₀ of 700 rads for the mouse
used in these experiments. Radioactivity in the cells is the
50-100 rad range with both cell and DNA.

The primary concern for irradiation of human populations is with genetic
and hematopoietic effects. The results of this study are consistent
to situations where humans are exposed to significant, but not lethal,
radiation doses.

Abstract: none.

EFFECT OF MICROWAVES ON ENZYMES

Albert P. Sheppard

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RL 00412-02

Project Description and Objectives: To investigate the effects of radiation of frequency 0.1 megacycles to 1000 megacycles on protein.

Significant Results: A sample of buffered lysozyme or trypsin was irradiated with microwaves. A second sample was heated by a coil to the same temperature as the former. An unheated sample was the control. Subsequent enzyme assays showed significant inactivation in the two kinds of samples heated to above 60°C for two hours. Microwave heated and coil-heated samples showed the same degree of inactivation. Thus, they found no evidence for anything other than purely thermal effects of microwaves on enzymes.

They are building the necessary equipment to study the effects of megacycle range radiation on enzymes.

Publications: Huddleston, G. K., J. B. Langley, A. Sheppard, and E. Yeagers, "The Effects of Microwaves on Equipment," Proceedings of the 1972 Purdue Symposium on Electromagnetic Hazards, Pollution and Environmental Quality, Lafayette, Indiana (May 8-9, 1972).

Abstract: The effect of nickel on the growth of the plant *Phaseolus vulgaris* L. was studied. The results show that nickel has a stimulatory effect on the growth of the plant.

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CURRENT TRENDS IN SURVIVORSHIP
OF RADIOLOGISTS

Genevieve M. Matanoski
Johns Hopkins University
Baltimore, Maryland

RL 00433-02

Project Description and Objectives: The study design of the project compares the mortality of a cohort of physicians specializing in radiology to that of five other types of specialists. All are identified by the year of entry into a specialty society beginning with the data from a previous study by Drs. Seltser and Sartwell which established the membership rosters of these organizations from about 1915 through 1954. It is the plan of the current study to update that original population, adding new entries into the five specialty societies beginning with 1955 and determining the present status of the original membership. The specific aims of the study are:

1. To determine whether ionizing radiation is currently producing life-shortening effects in exposed physicians.
2. To determine whether current safety measures have reduced the hazards of radiation in the newer members of the specialty.
3. To examine the underlying cause of death to see whether radiologists still have an increased risk of dying of leukemia and other forms of cancer.
4. To utilize multiple and contributory causes of deaths in order to better quantitate the overall risk of a specific disease in radiologists as compared to other specialists.

Significant Results: At the present time, the updating of information on 3 of the societies is completed. These societies include the radiologists (RSNA), the opthaalmogists and otolaryngologists (AAOO), and the orthopedic surgeons (AAOS). A preliminary comparison of the age-specific mortality of the RSNA and the AAOO revealed that the excess mortality for radiologists does not appear until age 55 for the cohorts entering the societies before 1955. The excess risk of death then continues into the older ages. The mortality ratios for the age groups 50-64 and 65-79 are 1.1 and 1.3 respectively for the calendar time period 1955-64. A recent analysis of the age-adjusted death rates for all cancers revealed that the mortality ratios for this specific group of diseases in the same age groups are 2.5 and 1.3.

Although the data are still preliminary, an initial analysis suggests that for radiologists who have joined the specialty from 1915 through 1954, and who have lived to the ages of 50 or more during the three decades beginning in 1935 and ending in 1964, a small but persistent excess risk of mortality exists. The excess risk which is attributable to cancer is probably not sufficiently large to account for all of the difference in mortality.

Publications: None.

BASIC EFFECTS OF MICROWAVES
IN BIOLOGICAL SYSTEMS

Alan Van Heuvelen
New Mexico State University
Las Cruces, New Mexico

RL 00480-02

Project Description and Objectives: The overall objective of this work is to determine if microwaves cause non-thermal biochemical effects. If effects are observed, the frequency and intensity dependence of the effects will be studied.

Enzyme kinetics and enzyme systems are being analyzed using microwaves ranging in power from 0 to several watts and in frequency from 10 mHz to 10GHz. The main tools being used are optical spectroscopy, electron paramagnetic resonance (EPR) and electron double resonance (ELDOR). Non-thermal effects of microwaves under consideration are: conformational changes in proteins; changes in protein mobility in polar solvents due to the presence of microwaves; selective absorption of microwaves by vibrational modes in proteins; orientational effects of microwaves on enzymes; and others.

Significant Results: This project has been funded for only one year. During that time much effort has been spent in building equipment. An optical system has been built for monitoring enzyme reaction rate changes caused by microwaves. They have also done some work in automating their electron double resonance (ELDOR) apparatus.

In addition to building equipment they have been able to make some preliminary measurements on two enzyme systems. They have used the optical equipment to look for enzyme reaction rate changes caused by microwaves for the enzymes tyrosinase and alcohol dehydrogenase. Microwave frequencies used have been 10-50mHz and 8-10GHz. Microwave power of one watt or less has been used. They have to date observed no microwave dependent effects on enzyme reaction rates.

Publications: None.

RADIOIODINE DOSIMETRY IN
THYROTOXICOSIS

A. Bertrand Brill
Vanderbilt University
Nashville, Tennessee

RL 00511-01

Project Description and Objectives: The project is designed to produce estimates of the absorbed radiation dose received by thyrotoxic patients given diagnostic and therapeutic doses of I-131. The patient material is derived from the cooperative thyrotoxicosis therapy follow-up sponsored by the USPHS-Bureau of Radiological Health. A time varying model of iodine kinetics is being fitted using Berman's SAAM-25 program. An attempt will be made to relate the derived parameters and radiation doses to severity of the disease and the outcome of therapy.

Significant Results: Project started in May 1972. The work to date has focused on the development of a mathematical model which is adequate for both therapy and diagnostic doses. The initial studies have been carried out on selected study patients who have been studied over a prolonged time period. The results of the first 3 months efforts indicate the approach is sound, and useful results should be forthcoming.

The results of this study will contribute to two separate questions.

1. I-131 dosimetry in patients treated with radioiodine for thyrotoxicosis.
2. Radiation injury to be expected from large dose accidental exposures from radioiodine.

Publications: None.

THE CYTOGENETICS OF URANIUM MINERS
EXPOSED TO $^{222}\text{RADON}$

William F. Brandom
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Denver, Colorado

RL 00520-02

Project Description and Objectives: High-energy alpha particles from short-lived $^{222}\text{Radon}$ daughters cause a significant increase in the incidence of lung cancer in uranium miners. The objectives of the study are: (1) to determine the kinds and frequency of somatic cell mutations caused by long-lived radon daughters in non-lung cells (leukocytes), (2) determine whether there is a relationship between estimated cumulative radiation exposure and the prevalence of chromosomal changes and, (3) to evaluate the persistence of cells with aberrant chromosomes after cessation of uranium mining.

Significant Results: They have cultured the leukocytes of over 200 uranium miners and age-matched controls. Work and medical histories have been gathered on all individuals. Chromosomal analyses (numerical and structural changes) have been completed on 140 individuals from this population. The results from 30 uranium miners and controls are in press. In the initial report it was concluded that the uranium miners as a group significantly exceed the controls in all categories of numerical and structural chromosomal changes. New findings have resulted from the analysis of the increased population. The subjects are grouped into 4 groups according to estimated cumulative exposure expressed in Work Level Months (WLM: I >0-499; II 700-1400; III 1600-2900; and, IV >3000). Comparison of the prevalence of chromosomal aberrations between miners of the above exposure categories reveal differences between the groups. There is a linear increase in aberration frequencies in Groups I, II, III. There is no further increase in chromosomal aberration frequency with radiation exposure in excess of 2900 WLM. The majority of the miners in Group IV ceased mining years ago (av. time - 6.8 yrs.). Perhaps post-mining selective loss of some cells containing particular kinds of aberrations accounts for the plateau dose-response effect. There is indirect evidence that some chromosomal aberrations survive longer *in vivo* than others. Inter- and intra-chromosomal exchanges are of two types: (a) symmetrical (reciprocal translocations and inversions) and, (b) asymmetrical (dicentric and ring chromosomes). The probability of the occurrence of symmetrical exchanges is significantly greater than asymmetrical exchanges (more than twice), indicating selective deaths of cells containing asymmetrical exchanges.

Uranium miner cells have a greater prevalence of chromatid (sub-chromosomal) aberrations (breaks, deletions, minutes, and exchanges) than do the control cells. There is no correlation between the prevalence of chromatid aberrations and estimated cumulative exposure groups.

Current uranium miners show a greater prevalence of chromatid aberrations than do uranium miners who have ceased uranium mining (0.030/cell vs 0.015/cell). Chromatid aberrations are supposedly induced during the late-S or G₂ phases of the cell cycle. *In vivo* peripheral blood lymphocytes are in the G₀ or G₁ stage of the cell cycle. Thus, the chromatid aberrations that we observe after *in vitro* culture have either been induced in culture or may have been induced by an indirect effect of radiation, the postulated "plasma factor."

In summary, significant increases were observed in chromosomal aberrations in uranium miners vs age-matched controls. A linear increase was observed in chromosomal aberrations with increasing radiation exposures up to 2900 WLM. Cells containing symmetrical chromosomal exchanges survive longer *in vivo* than cells containing asymmetrical exchanges. Chromatid aberrations are more prevalent in miners who are currently mining than in miners who have ceased mining. All analyses of the 14,000 cells in this study were done without prior knowledge of individual histories. It is premature to assess the late-effect, health hazards from these anomalies.

Publications: None.

RADIATION DAMAGE METABOLISM IN
REPRODUCTIVE SYSTEM

Valerio Monesi
University of Rome
Rome, Italy

RL 00526-03

Project Description and Objectives: The general objective of the research project is to investigate the effects of ionizing radiation on the mitotic and meiotic cycles and to study those molecular events which might control the sensitivity to radiation damage and the repair mechanisms at definite stages of the mitotic cell cycle and germ cell development. The study will involve a biochemical analysis of macromolecular synthesis during mitosis and meiosis in the mouse and the evaluation of some radiation effects on somatic and germ cells.

Significant Results: The research work has developed along the following lines: (1) Characterization of macromolecular synthesis and metabolic requirements during early embryogenesis in the mouse. This work has shown that RNA is synthesized very soon after fertilization and that these RNA molecules are immediately requested to support embryonic development and protein synthesis by the embryo. However, our work suggests the possibility that a fraction of protein synthesis during early development might be dependent on stable RNA molecules synthesized during oogenesis. This fact might be relevant for the radiation sensitivity of the early embryo to ionizing radiation. (2) Analysis of molecular events during differentiation of male and female germ cells which might affect the radiation sensitivity of the repair mechanisms. It was found that the genetic inactivation of the spermatid nucleus is accompanied by the arrest of synthesis of nuclear proteins and the elimination of most macromolecular components from the chromosomes except the DNA and the histone. Spermatid development after this stage is regulated by stable RNA molecules synthesized in meiosis. These metabolic changes are most likely very important factors for the radiation response of germ cells and for the subsequent embryonic development after irradiation at definite stages of gametogenesis. Another work under progress indicates that in mouse spermatocytes the nucleolus is inactive in ribosomal RNA synthesis. On the other hand spermatocytes do contain radioactive rRNA after short labeling with ^{32}P . One possible explanation of these findings is that the rRNA present in spermatocytes is transferred from the Sertoli cytoplasm.

A third line of research still under progress is aimed to study those molecular events (stable RNA molecules?) in mouse oogenesis which might affect early embryonic development following fertilization of irradiated oocytes.

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BRACON, AN ASSAY FOR GENETIC
EFFECTS OF MICROWAVES

Lawrence R. Valcovic
Auburn University
Auburn, Alabama

RL 00527-01

Project Description and Objectives: To assay the genetic and physiological effects of 2450 MHz radiations using the parasitic wasp, *Bracon hebetor*. Experiments are designed to survey mature sperm and all stages of oogenesis for mutational effects, particularly dominant lethality, recessive lethal and visible mutation frequencies, and inherited partial sterility. Additional data will be collected on life span and heritable biochemical differences as detected by starch gel electrophoresis.

Significant Results: Adult females were irradiated at 200 mW/cm^2 for 30, 60, 90, 120, and 150 minutes. Life span, fecundity, and fertility of irradiated females was not significantly different from control data.

Publications: None.

Journal of the
American Chemical Society
Vol. 71, No. 1, 1949

BRADY, W. L. and
GILBERT, R. L.
EFFECTS OF ELECTRICITY

RECEIVED 1948-12-15

Abstract: The effect of electric fields on the rate of reaction between hydrogen peroxide and ferrous sulfate was studied. The rate of reaction was found to be increased in a magnetic field and decreased in an electric field. The effect of the electric field was found to be dependent on the concentration of the reactants. The effect of the magnetic field was found to be independent of the concentration of the reactants. The effect of the electric field was found to be dependent on the concentration of the reactants. The effect of the magnetic field was found to be independent of the concentration of the reactants.

Keywords: Hydrogen peroxide, ferrous sulfate, electric field, magnetic field, reaction rate, concentration, rate of reaction, effect of electric field, effect of magnetic field, dependence of rate on concentration, independence of rate on concentration.

References: None.

QUANTITATIVE EFFECTS OF EM ENERGY
ON HUMAN TISSUES

Arthur W. Guy
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RL 00528-03

Project Description and Objectives: To study theoretically and experimentally the interaction of electromagnetic (EM) radiation with biological structures to aid in the development of realistic guidelines and safety standards. Of primary interests are the quantifiable effects of human exposure to EM energy as related to the source frequency, configuration, location and field strength. This would involve controlled exposure of test animals to selected sources of EM energy at both low and high levels while monitoring the energy in the tissues. Physiological characteristics (i.e., evoked central nervous system responses) of the animals will be observed before, during, and after exposure to the EM sources. Through the use of theoretical and thermographic models it is the intent to establish quantitative extrapolation between human and animal exposures. Furthermore, it is intended to evaluate the design of diathermy machines in current clinical usage. Any potentially hazardous defects will be noted and corrected to make the equipment safe and still therapeutically beneficial to the patient.

Significant Results: Exposure of cat's head to 918 MHz microwave irradiation was found to induce increases in brain temperature with maximum change occurring in the thalamus and hypothalamus region. The temperature increase was accompanied by a decrease in latency time of late components of the evoked responses to electrical stimulation of somatosensory receptors in the cat's contralateral forepaw and auditory stimuli. The fields and associated heating patterns were found to have maximum amplitudes near the center of the brain. This is accomplished through the use of thermocouples on live cats as well as the use of thermographic recordings on half sections of dead cats. When the maximum heating intensity approached 5 mW/cm^3 significant changes in the characteristic of evoked central nervous system response, (i.e., reduction of latency and/or in amplitude) were observed and measured. These same effects were also found when the cat was exposed to energy levels corresponding to the American National Standards Institute safety level of 1 mW hr/cm^2 . The maximum energy absorption in the cat's brain due to each of these exposures was 0.3 to 1 mW hr/cm^3 . Calculation made on spherical models of human and animal heads and bodies indicate that for a given incident power the internal power absorption can vary by orders of magnitude with body size and frequency. In addition, it was found that the mammalian head resonates at certain microwave frequencies which explains clearly the observed temperature maxima in the center of the cat's brain.

The choice of recording electrodes of different composition was observed to be of crucial importance. Fluid filled glass electrodes of ionic concentration other than Ringer's solution (say 4 molar), when irradiated with EM energy were found to produce artifacts as data. This effect may be due to driving ions out of the recording electrodes into the vicinity of cells, thus affecting their excitability. Insulated metal electrodes have also been found to yield unorthodox responses.

Publications: Johnson, C. C. and A. W. Guy. Nonionizing Electromagnetic Wave Effects in Biological Materials and Systems, Proc. IEEE, 60(6):692-729, (1972)

RESEARCH ON CUMULATIVE MICROWAVE
RADIATION EXPOSURE

Richard W. Grow
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Salt Lake City, Utah

RL 00534-01

Project Description and Objectives: The objective of this project is as follows: To make a frequency-insensitive and orientation-insensitive microwave power detector, to integrate the detected power to measure cumulative exposure, and to obtain reliability in an instrument that is small enough to be worn on the person. Both theoretical and experimental research are being conducted to find ways to solve these problems. Some specific methods for measuring cumulative exposure that are being investigated are based on electrochemical coulometers, capacitor chargers, and digital counters to integrate the exposure with time.

Significant Results: Microwave devices have been widely used in the military services and in civilian applications for about 30 years, and personnel exposed to microwave radiation have suffered burns that were slow in healing because of the depth of penetration. Despite this known hazard, researchers, development engineers, and technicians have observed only a few safety procedures; i.e., avoiding looking down open-ended waveguide, staying away from a high-power antenna, etc. Beyond these obvious rules, however, a "can't hurt me" attitude persists. Microwave ovens threaten to change the number of possible exposures, and the construction of very high-power antenna facilities in areas where exposure to the populace is possible have increased the hazard. In the past, little effort has been expended on constructing a device specifically designed to measure low-power cumulative exposure. This is the object of the present project.

In the case of ionizing radiation, film badges and radiation pens have been used for years. It is in analogy to the ionizing radiation pen that the present work was conceived. The specific objective will be to produce such a cumulative radiation dosimeter. The wearing of such a pen would become routine among factory workers exposed to microwave radiation and it would also become routine for personnel working around such hazards.

It is envisioned that the instrument will be placed adjacent to the person, perhaps in the shirt pocket, and the antenna will be able to measure the square of the electric field intensity at the surface. Thus, the instrument will measure a quantity proportional to power and integrating the power will give the total energy flowing into the person wearing the dosimeter.

Design of the first prototype has been completed and construction of a prototype is in process. The prototype consists of three short, orthogonal dipole antennas, square-law diode detectors, and a microcoulometer. The three orthogonal antennas and square-law detectors act to pick up the radiation and detect it, producing a signal proportional to the incident power. The microcoulometer is an integrating device which consists of an electrolytic bubble in a mercury column in a capillary tube. The detected radiation produces a dc current, which is integrated and registered by the microcoulometer, thus providing a reading of the total energy to which the meter has been exposed. The whole device can be made small enough to fit inside an ordinary pen, and it can be made rugged enough to be very practical.

Publications: None

AUTOMATED CYTOGENETIC RADIATION
HEALTH MONITORING

Niel Wald

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RL 00575-02

Project Description and Objectives: The goal of this project is to develop an automatic cytogenetic analysis system for radiation health monitoring purposes in order to make feasible the use of readily generated quantitative information concerning chromosome aberrations in appropriate populations. Such populations include workers in the nuclear industry, members of the public inadvertently exposed to accidentally released radioactivity, people whose living environment is demonstrated to contain a higher level of radioactivity than the usual and individuals undergoing medical x-ray or radioisotope exposure. Cultured cells or populations exposed to other clastogens (chromosome breaking agents) can also be studied this way. The project involves the development of an automatic microscope to scan blood cell cytogenetic slide preparations, locate dividing cells and collect the information by flying spot scanner in a computer-compatible form; systems engineering to control the microscope with a PDP-7 computer and to transfer the information to a PDP-10 computer system; and software development for storage, manipulation, and analysis of cytogenetic data, as well as its correlation with environmental exposure and health data of the populations under study.

Significant Results: In the six months since this project began, developments have commenced in two main areas. These are automatic location of mitotic peripheral blood cells; and computer identification of the important radiation-related chromosome aberrations.

For mitotic cell location the investigators have begun the modifications needed to improve the performance of our automatic microscope which uses a laser to generate diffraction patterns of objects on the usual cytogenetic slide preparation. Utilizing a new combination of mitotic cell recognition criteria involving scattered light and cell width measurements, the investigators were able to reject 98 percent of artifacts while finding all the mitotic cells in a preliminary test set. Also, it was found that 76 percent of the mitotic cells below the mean width had overlapping chromosomes compared to 39 percent of those above, permitting rejection of the majority of cells unsuitable for cytogenetic analysis because of overlap. In addition, tentative alterations in the location and aperture of the substage condenser assembly appear to provide a marked gain in resolution for subsequent image data extraction.

For computer recognition of major radiation-induced aberrations (rings, dicentrics, and fragments) they are doing some preliminary investigation of a scheme of two-level classification. In the first level, they have used three parameters, namely, integrated optical density, ratio of the

moment about the principal axis to that about the minor axis, and perimeter squared divided by area, to sort out chromosomes into three classes and to pick out candidates for classification as fragments, dicentrics and rings. In the second level, using Fourier transforms of the two intensity profiles of each object, they have identified some distinctive attributes in the Fourier spectra which can be used to perform feature extraction for distinguishing the abnormal chromosomes from the normal ones.

Publications: None.

EFFECTS OF MICROWAVES ON CNS,
LIVER, AND HEART

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RL 00583-01

Project Description and Objectives: The overall objective is to determine the nature and extent of reversible and irreversible effects in biological tissues (CNS, Heart, and Liver) after irradiation with microwaves of 2450 MHz at power densities of 5 - 50 mW/cm². The observations are being made with the electron microscope and ultrastructural morphology correlated with biochemical determinations (ATP utilization and protein synthesis).

Significant Results: Microwaves are increasingly being used in communication, industry, home, and military and as a result large numbers of the American people are daily exposed to microwave radiation. The biological effects of microwaves are at best very poorly understood. The lack of knowledge about the biological effects of microwaves manifests itself in the disparity between safety standards of the Soviet block and the United States. The USA allows a continuous exposure of 10 mW/cm², while the USSR and Poland allow .01 mW/cm².

The approach used by this investigator is unique and significant in that very early changes that occur at the macromolecular or subcellular level can be recognized only with the electron microscope. These early changes cannot be observed at the light microscope resolving power unless the changes have progressed considerably. Our experiments have thus far revealed that nonionizing radiation at 50 mW/cm² (2450 MHz) causes several alterations in the cellular organelles of hamster heart and liver after one hour of exposure. Specific changes thus far observed are in mitochondria and their cristae, smooth and rough endoplasmic reticulum.

The mitochondria are responsible for about 90% of the total energy produced in the body. The rough endoplasmic reticulum is primarily responsible for protein synthesis and the smooth reticulum is associated with hormone synthesis, ionic transport, cholesterol metabolism, etc. We have thus far correlated the morphological changes in liver mitochondria after one hour of exposure with total production of ATP (energy source) and found that there is no change in oxydative phosphorylation (ability to produce energy). Our future studies will deal with exposures at lower power densities (5 - 10 mW/cm²) and for longer duration (8 hours - days).

Publications: None.

The first study was conducted by the author and his colleagues in 1955. It was a longitudinal study of 100 subjects with hypertension. The subjects were divided into two groups: 50 who were treated with medication and 50 who were not. The study was designed to determine the nature and extent of hypertensive and associated changes in biological tissues (liver, heart, and kidney) after treatment with antihypertensive drugs. The subjects were followed up for a period of 10 years. The results of the study showed that the subjects who were treated with medication had a significantly lower mortality rate than those who were not treated. The subjects who were treated also had a significantly lower incidence of hypertensive complications, such as stroke, heart failure, and kidney disease. The study also showed that the subjects who were treated had a significantly lower incidence of liver disease, such as cirrhosis and liver cancer. The study concluded that treatment with antihypertensive drugs significantly reduces the risk of mortality and morbidity in subjects with hypertension.

Subsequent studies have confirmed the findings of the first study. In a study conducted by the author and his colleagues in 1960, 200 subjects with hypertension were followed up for a period of 10 years. The subjects were divided into two groups: 100 who were treated with medication and 100 who were not. The study showed that the subjects who were treated with medication had a significantly lower mortality rate than those who were not treated. The subjects who were treated also had a significantly lower incidence of hypertensive complications, such as stroke, heart failure, and kidney disease. The study also showed that the subjects who were treated had a significantly lower incidence of liver disease, such as cirrhosis and liver cancer. The study concluded that treatment with antihypertensive drugs significantly reduces the risk of mortality and morbidity in subjects with hypertension.

The approach used by this investigator is unique and revolutionary in that it is the first study to have been conducted in which the subjects were followed up for a period of 10 years. This is a significant achievement, as most studies of hypertension are conducted in which the subjects are followed up for a period of 5 years or less. The study also shows that the subjects who were treated with medication had a significantly lower incidence of liver disease, such as cirrhosis and liver cancer. This is a significant finding, as liver disease is a common complication of hypertension. The study also shows that the subjects who were treated with medication had a significantly lower incidence of heart failure and kidney disease. This is a significant finding, as heart failure and kidney disease are common complications of hypertension. The study concluded that treatment with antihypertensive drugs significantly reduces the risk of mortality and morbidity in subjects with hypertension.

The investigator has also conducted a number of other studies on the effects of hypertension on the liver and heart. In a study conducted in 1965, the investigator followed up 100 subjects with hypertension for a period of 10 years. The subjects were divided into two groups: 50 who were treated with medication and 50 who were not. The study showed that the subjects who were treated with medication had a significantly lower mortality rate than those who were not treated. The subjects who were treated also had a significantly lower incidence of hypertensive complications, such as stroke, heart failure, and kidney disease. The study also showed that the subjects who were treated had a significantly lower incidence of liver disease, such as cirrhosis and liver cancer. The study concluded that treatment with antihypertensive drugs significantly reduces the risk of mortality and morbidity in subjects with hypertension.

STUDY OF GENETIC EFFECTS OF
MICROWAVE RADIATION

Frank P. Hungate
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Battelle Memorial Institute
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RL 00688-02

Project Description and Objectives: The projected research will evaluate mutation rates induced following exposure to 2450 HZ₃ microwave radiation and establish a basis by which the mutation rate can be related to the energy absorbed at the sensitive site.

Microorganisms will be used since they afford both a sensitive test system and ease of manipulation within the exposure chamber.

Absorbed dose will be evaluated by measuring temperature change under conditions favoring heat flow from the cells to the suspending medium as well as the reverse. Intracellular biochemical transformation sensitive to temperature change will be utilized to relate energy status of the intracellular microenvironment to the macroenvironment of the cell suspensions.

Results of these studies will be used to assist in establishing safe limits for exposures to microwaves. It is also anticipated that this study will help in our general understanding of the interactions of electromagnetic radiations with living systems.

Significant Results: The project is in progress. At this time the basis for measuring absorbed dose is established and the mutation induction phase of the research is being initiated.

Publications: None.

NCI 00088-01

Protein denaturation and aggregation. The proposed program will evaluate
nutrient rates induced following exposure to 2.45 GHz microwave radiation
and establish a basis by which the nutrient rate can be related to the
energy absorbed at the sensitive site.

Microorganisms will be used since they afford both a sensitive test system
and ease of manipulation within the exposure chamber.

Absorbed dose will be evaluated by measuring temperature change under
conditions favoring heat flow from the cells to the surrounding medium as
well as the reverse. Theoretical biochemical calculations as well as
to temperature change will be utilized to relate energy absorbed to the
intracellular microenvironment to the microenvironment of the cell
membranes.

Results of these studies will be used to assist in establishing safe limits
for exposure to microwaves. It is also anticipated that this study will
help in our general understanding of the nature of electromagnetic
radiation with living systems.

Significant Results: The program is in progress. As this is the first
for research absorbed dose is established and the various conditions
phase of the research is being initiated.

Publication: None.

RADIATION QUANTITIES, UNITS AND
MEASUREMENT TECHNOLOGY

W. Roger Ney
National Council on Radiation
Protection and Measurements
Washington, D.C.

RL 00695-01

Project Description and Objectives: The International Commission on Radiation Units and Measurements (ICRU), has as its principal objective the development of internationally acceptable recommendations regarding: (1) Quantities and units of radiation and radioactivity, (2) Procedures suitable for the measurement and application of these quantities in clinical radiology and radiobiology, (3) Physical data needed in the application of these procedures, the use of which tends to assure uniformity in reporting.

The Commission also considers and makes similar types of recommendations for the radiation protection field.

The ICRU endeavors to collect and evaluate the latest data and information pertinent to problems of radiation measurement and dosimetry and to recommend the most acceptable values for current use.

Significant Results: Work was completed on two reports -- Radiation Dosimetry: Electrons With Initial Energies Between 1 and 50 MeV and Measurement of Low-Level Radioactivity -- and they were published as ICRU Reports 21 and 22 respectively. The work on the report "Measurement of Absorbed Dose in a Phantom Irradiated by a Single Beam of X or Gamma Rays" was also completed and the report is now being prepared for the printers. It is expected that the report will be published late in 1972. The Commission determined that a companion report dealing with the measurement of absorbed dose in a patient should be accelerated, with the hope that the work can be completed within the next fifteen months. The preparation of reports on the following topics continues -- dose specification for reporting, modulation transfer function: its definition and measurement, scanning of internally deposited radionuclides, methods of assessment of dose in tracer investigations, dosimetry in radiobiology high energy and space radiation dosimetry, neutron dosimetry for biology and medicine, and average energy required to produce an ion pair.

At its recent meeting, the Commission examined various proposals for new Commission activities and determined to begin a new study aimed at the development of a report on concepts and principles of radiation protection measurement. Related to this new program is the Commission's decision to study the dimensions of quality factor. This new task was assigned to the Committee on Quantities and Units. At the recent meeting the Commission also determined to undertake preparatory work necessary to

the initiation of a comprehensive study of stopping powers.

In activities not related to the development of ICRU Reports, the Commission began an examination of the implications of the proposed elimination of the special radiation units -- roentgen, rad, rem and curie. The Commission also examined the recently published proposal that exposure-area product be used in the assessment of patient irradiation during diagnostic procedures and formulated a brief statement on this topic advising against the adoption of a special unit for this quantity and emphasizing the deficiencies of this quantity for the assessment of risk in diagnostic radiology.

Publications: None.

RL 00726-01

Project Description and Objectives: The objective of this study is to determine whether levels of ionizing radiation received by a female fetus in the course of diagnostic x-ray procedures such as pelvimetry will affect her ovaries and germ cells to an extent that would have an observable effect on her subsequent reproductive performance.

The study population comprises 1458 females exposed to x-ray during fetal life (when their mothers had pelvimetry or other procedures) matched with 1458 unexposed controls by hospital of birth, parity, and birthdate. All are black, born in Baltimore in 1947-1952, and all are still residents of Baltimore City. Births to members of the study population are ascertained by matching their maiden names with those of mothers on the Baltimore City birth certificates of appropriate race, age, and birthplace.

Significant Results: Pregnancies that occurred through 1970 have been ascertained. At the end of 1970 the in-utero exposed and their unexposed controls were aged 18-23 and had given birth to 2,450 babies. Preliminary analysis of births through 1969 showed significantly higher pregnancy rates among exposed mothers than among controls, including live births, fetal deaths, and abortions. Recent findings suggest that this excess fertility among exposed mothers begins to decline at age 18, as fetal and infant mortality increases. Animal studies show that the effect of radiation on fertility varies enormously with the time of exposure during fetal life or in infancy. They have therefore analysed their data by the gestational age of the female fetus when she was exposed. The most significant difference in fertility rates has been observed in the group x-rayed at 35-37 weeks. More stringent analytic methods are now being applied to the data, and 1970 births are in process of analysis.

This is the only existing study of humans exposed to x-ray in utero with matched controls, who are now being followed for second generation effects. If significant differences in fertility and mortality patterns are found, or if differences in congenital malformations or other problems are found in either the first or the second generation, the frequency or timing of x-ray pelvimetry might be altered. The use of abdominal x-ray during pregnancy has already been curtailed because of known effects on the unborn child during early gestation. If this study shows that the fetal ovaries, germ cells, and future offspring are affected, even further curtailment of x-ray use may be indicated.

Publications: None.

THERMOLUMINESCENCE ULTRAVIOLET
RADIATION DOSIMETRY

William G. Buckman
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Bowling Green, Kentucky

RL 00733-01

Project Description and Objectives: The objective of this investigation is to develop an ultraviolet radiation dosimeter that utilizes the thermoluminescence properties of materials.

The thermoluminescence (Tl) properties of materials are now widely used for detecting high energy ionizing radiation. The necessary equipment for measuring thermoluminescent of materials is widespread. It is well-known that ultraviolet (uv) radiation produces deleterious effects on man such as erythema, painful inflammation of the membrane of the eye (conjunctivitis), and skin cancer. Ultraviolet radiation is constantly in our environment due to uv components of terrestrial solar radiation, electronic production of uv radiation by germicidal lamps for disinfection, lasers, and numerous other applications in therapy and technology. Recognizing the hazards of exposure to radiation from germicidal lamps the Council on Physical Medicine and Rehabilitation of the American Medical Association has set a low tolerance limit of $0.1 \frac{\mu \text{ watts}}{\text{cm}^2}$ for continuous exposure.

Significant Results: They have found that aluminum oxide containing titanium as the luminescent center has Tl characteristics favorable for ultraviolet radiation dosimetry and a patent application has been filed. With this material one has a simple portable dosimeter (about 1 millimeter³) that can measure extremely low levels ($< 0.1 \frac{\mu \text{ watts}}{\text{cm}^2}$) of ultra-

violet to high levels of radiation. It responds linearly with exposure and is exposure rate independent. Investigations are continuing on this material. Recently our research has shown that lithium fluoride, which is pre-irradiated to 400,000 roentgens of Cobalt-60 gamma radiation and then thermally annealed to 300°C, can be photo-stimulated with germicidal lamps. The response is linear to above $200 \frac{\mu \text{ watts}}{\text{cm}^2}$ and exposure rate independent to $200 \frac{\mu \text{ watts}}{\text{cm}^2}$. Since this

material is now used in medical centers for x- and gamma radiation, it only appears to require a high x-ray or gamma exposure to make it a practical ultraviolet radiation dosimeter. Calcium fluoride containing europium has response characteristics favorable to ultraviolet radiation dosimetry and these experiments are now in progress

Publications: None.

CELLULAR DAMAGE BY VISIBLE AND
NEAR-VISIBLE LIGHT

Abraham Eisenstark
University of Missouri
Columbia, Missouri

RL 00748-01

Project Description and Objectives: They have found bacterial mutants that are highly sensitive to visible and near-visible light. These mutants also have the interesting property of inability to undergo genetic recombination (i.e., they are recombinationless mutants). The broad research objectives are: (a) To identify the molecular aberration that accounts for the high sensitivity and mutation, (b) To determine whether any light absorbing molecules in the cell have a role in normal chromosomal replication and recombination, and (c) To determine effect of tryptophan photoproduct on cells.

Significant Results: L-tryptophan, upon exposure to light, becomes toxic for recombinationless (rec) mutants of *Salmonella typhimurium*. The toxic component is a photooxidation product, since it is formed only under aerobic conditions. Other amino acids and sugars were tested, but the toxic property was found only for light-exposed tryptophan. A number of tryptophan derivatives were examined for specific toxicity for rec cells, but none were found to be as effective. An action spectrum of the maximum yield of phototoxin reveals 290 nm to be most effective, with a range of 270 to 360 nm. The photoproduct is active on rec strains but it does not kill other UV-sensitive strains, such as those that have uvr or hcr mutations. Also, the photoproduct inactivates rec mutants of *Escherichia coli* and *Bacillus subtilis*. In addition to toxicity, the tryptophan photoproduct is also mutagenic. Isolation and identification of the active photoproductive is now underway. These results are consistent with previous observations of sensitivity of recombinationless mutants to UV, near-UV and visible light.

Publications: None.

1925-26

... investigation and observation. They have found bacterial mutants that are highly sensitive to visible and near-visible light. These mutants also have the interesting property of being able to undergo genetic recombination (i.e., they are recombinogenic mutants). The first research objectives are: (a) to identify the mutants responsible for the high sensitivity and resistance, (b) to determine whether any light absorbing molecules in the cell have a role in the photosynthetic reaction and transduction, and (c) to determine effects of various photosynthetic on cells.

... investigation of the mutants, upon exposure to light, showed that for photosynthesis (i.e., mutants of *Rhodospirillum rubrum*) the main component is a photosynthetic product. Some of the mutants may have other metabolic conditions. Other mutants show high resistance to light, but the basic property was found only for light-resistant mutants. A number of cytoplasmic derivatives were examined for specific resistance for red cells, but none were found to be as effective as the action spectrum of the mutants. The photosynthetic action spectrum is most effective with a range of 170 to 260 nm. The photosynthetic action spectrum is not active but it does not kill other photosynthetic mutants, such as those that have been reported. Also, the photosynthetic mutants are mutants of *Rhodospirillum rubrum* and *Rhodospirillum rubrum*. In addition to this, the cytoplasmic derivatives in the mutants and identification of the active photosynthetic is now under investigation. These results are consistent with previous observations of sensitivity of photosynthetic mutants to ultraviolet and visible light.

References:

BEHAVIORAL AND NEURAL EFFECTS OF
RADIATION AND TOXINS

John Garcia*

Research Foundation of the
University of Utah
Salt Lake City, Utah

RL 01019-01

Project Description and Objectives: Ionizing radiations produce two behavioral effects upon experimental animals (and human patients). First, ionizing rays mimic an odorant by stimulating the olfactory mucosa. Animals cope with this stimulus by alerting and orienting. This effect coincides with the very onset of exposure and produces the characteristic electroencephalographic changes which attend arousal. Second, radiation exposure produces an after-effect which mimics the effect of illness induced by a toxin. The animal attempts to cope with this insult by changing its feeding habits. The research is directed towards elucidating the behavioral and neurological implications of adaptive behavior to this toxin-like effect of radiation.

Significant Results: Previous results have indicated that the noxious effects of radiation can be induced in non-irradiated rats by injections of serum from irradiated donors, by injections of emetic drugs or nitrogen-mustard compounds, or by ingestion of a toxic (lithium salt) solution. In all cases animals develop a profound aversion for a new substance consumed before the illness as if they had eaten a "poison." This profound aversion for a flavor cannot be produced by peripheral pain, only by internal illness.

Present research indicates that recuperation from illness produces an effect in the opposite direction. The animals acquire an appetite or taste for flavors consumed prior to recuperation as if they consumed a "medicine." This means that animals need no special receptors to specifically avoid toxins and to locate nutrients such as vitamins. They need only this general capacity to associate tastes with internal illness or recuperation and thus they are able to avoid toxins and to select a "healthy diet". Therefore, it has been shown that an animal suffering from thiamine deficiency will acquire a taste for saccharin in that flavor is arbitrarily paired with a thiamine injection. The way animals relate flavors to internal states appear to be fundamentally different from the way they relate environmental signals to peripheral insults. First, they can form the flavor-illness association in a few trials even when the illness is delayed several hours after eating. They cannot form buzzer-shock associations, for example, unless the shock is delivered within seconds after hearing the buzzer.

Brain lesion studies have substantiated this duplex notion of internal and external functions. Lateral septal and ventral hippocampal lesions disrupt external (noise-shock) learning but enhance internal (flavor-illness) conditioning. Medial septal lesions have little effect on noise-shock learning but also enhance flavor-illness learning. Amygdaloid lesions disrupt conditioning in both spheres. Future research is aimed at distinguishing behavioral laws for control of the internal milieu as opposed to control of the external milieu.

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*The principal investigator transferred this project from the State University of New York at Stony Brook, Albany, New York (previously identified as RL 00132-04).

INITIATION OF STRESS ON FORMATION OF PROTEIN AGGREGATES

ROBERT A. HAYES
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ED 000000-00

The present study was designed to determine the effect of stress on the formation of protein aggregates. The results indicate that stress does indeed promote the formation of protein aggregates, and that the rate of formation is dependent on the type of stress applied. The results also indicate that the formation of protein aggregates is a reversible process, and that the aggregates can be broken down by the application of heat or other physical agents.

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RESEARCH GRANTS TERMINATED - FY 1972

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References: None.

RADIATION EFFECTS ON FORMATION
OF PROTEIN AGGREGATES

Herman R. Haymond

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Los Angeles, California

RL 00064-10

Project Description and Objectives: This study has been concerned with the effects of ionizing radiation on proteins in aqueous solution with emphasis on the radiation-induced changes in the immunochemical properties of human proteins. Isolated proteins and known mixtures of proteins have been irradiated under various conditions. The resultant changes in the physical and immunochemical properties of the proteins have been studied by gel chromatography, discontinuous electrophoresis, immuno-electrophoresis and ultracentrifugation.

Significant Results: Recent work has been related to the radiation-induced changes occurring in the physical and immunochemical properties of human albumin and immunoglobulin G, two of the most abundant components of serum, when irradiated as isolated proteins or as mixtures of the two. Irradiation of either protein in solution results in the formation of aggregates and fragments of that protein. Irradiation of mixtures results in mixed aggregates of the two proteins. The spectrum of products obtained is dependent on radiation dose, concentration of proteins, and the presence or absence of oxygen during irradiation. In addition to changes in molecular size there are also changes in electrophoretic mobility and immunochemical properties which indicate that radiation-induced alteration of intramolecular bonds can occur to change the charge or shape of a molecule without aggregation or fragmentation. The aggregates formed from more than one protein retain some of the antigenic properties of the original molecules, and also give distinct patterns in immunoelectrophoresis. The acquisition of new physical and immunological properties by a combination of two or more different human proteins as a result of irradiation is of potential importance in the study of radiation effects on living systems since living tissue is a mixture of many different substances, and one significant result of irradiation may be the formation of unusual combinations of ordinary molecules or their fragments.

Publications: None.

PROTECTION AGAINST RADIATION
DAMAGE TO CHROMOSOMES

Sidney Mittler
Northern Illinois University
DeKalb, Illinois

RL 00075-06

Project Description and Objectives: The purpose of the research grant is to obtain information about chemical substances that may protect chromosomes from radiation injury and to discover substances if possible to protect against mutations induced by radiation.

Significant Results: ATP injected in male *Drosophila* did protect an X ring chromosome from radiation induced loss in meiosis. However, exogenous ATP injections did not reduce the number of radiation induced sex-linked lethals nor did it reduce the percentage of translocations, deletions in the X chromosome, and did not decrease the amount of radiation induced crossing-over in the male. Calcium, magnesium, manganese ions, and hyper and hypotonic solutions were injected into the testis of *Drosophila* in an attempt to stimulate ATP synthesis and to reduce the number of radiation induced dominant lethals. N,N' dimethyl 4,4' dipyridinium chloride at concentration of 10 mg/liter did not protect against radiation induced dominant lethals in *Drosophila*, nor did 3.5 percent of dimethyl sulfoxide protect against γ -ray induced recessive sex-linked lethals.

Publications: Mittler, S., J. F. Arnesen, and U. Raymond, "Effect of Urethane and Colchicine on Radiation-Induced Chromosome Loss in Male *Drosophila*," *Int. J. Rad. Biol.*, 11(2):161-170 (1966).

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BIOLOGICAL EFFECTS OF LOW VELOCITY
VELOCITY ELECTRONS

George S. Sperti
St. Thomas Institute for
Advanced Studies
Cincinnati, Ohio

RL 00076-09

Project Description and Objectives: When x-rays strike matter they eject electrons. It is through studies on the biological effects of electrons that it is hoped to attain a better insight into the beneficial and harmful actions of radiant energy.

To accomplish these results the investigators have designed and built a high vacuum apparatus for the generation of a beam of electrons, the velocity and number of which can be determined. The beam is directed toward a target area in which organisms or their biochemical components are placed. Bombarded specimens are examined to determine the effects of the impinging electrons and attempts made to correlate the results with known effects of electromagnetic radiations.

Significant Results: The results of the experiments have led to the conclusion that electrons must reach a critical velocity before they produce their biological effects. These critical velocities are not the same for all organisms tested. For example, it has been found that *Staphylococcus aureus* and *Staphylococcus albus* are killed by electrons moving at a velocity of 6,600,000 miles per hour or higher, but not by electrons moving at any lower velocity even though the number of bombarding electrons is greatly increased. *Saccharomyces cerevisiae* (baker's yeast) is killed by electrons only if they move at a velocity greater than 25,000,000 miles per hour.

In a search for the method by which electrons produce their results on living matter, a study was made of the effects of electrons of different velocities on amino acids, essential constituents of all cells. So far no change has been observed in any amino acid which has been subjected to bombardment by electrons of velocities which were found lethal to microorganisms.

The investigators have also studied the effects of electrons on larger molecules, including enzymes such as catalase and trypsin, both of which were found to be inactivated by electrons. Since the amount of any cellular constituent being affected will depend on the depth to which the bombarding electrons will penetrate the cell, it was also necessary to investigate the depth to which electrons can penetrate molecules. From the results it was learned that electrons capable of killing cells are barely able to penetrate a thickness of a single molecule of trypsin.

As a result, it has been concluded that the lethal effects of low velocity electrons are brought about by action of the electrons on or near the surface of the cells and that their action may not be the result of a biochemical change, but may be physical, such as changes in membrane permeability or electrical properties of the cell.

It is hoped that when sufficient data have been accumulated it will be possible to attain better therapeutic results with X-rays; and radioactive isotopes alone or incorporated in molecules which can be taken up by the cells.

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THE AGE FACTOR IN RADIATION
SENSITIVITY IN MAMMALS

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RL 00082-06

Project Description and Objectives: The effect of age at exposure to a known cancer producing agent, such as ionizing radiation, has been used in different strains of mice to study the possible dependence of cancer risk on the dose (in single or repeated fractions; or accumulated chronically from internally deposited radioactive substances), and the number of cells at risk. Comparisons are made of the dose-response yields for myeloid leukaemia, and for the production of lung tumours.

For myeloid leukaemia, the actual number or a proportion of cells at risk, are measured, but the probability of detecting more than one cell rendered leukaemogenic in the animal is small. In contrast, the yield of lung tumours shows that the tumour number is dependent on individual non-interacting events in the total population exposed.

Significant Results: Leukaemia. Myeloid leukaemia can arise from the transplantation of a single leukaemogenic cell. Irradiation of the bone marrow cells, either in the host, or prior to transplantation into a bone marrow depleted recipient, has shown that the probability of leukaemia induction increases with increasing dose until a peak yield is reached; the dose at the peak varies with the age of the animal at exposure, as well as with the natural incidence of leukaemia. Comparable irradiation of bone marrow used for acute life saving studies in lethally exposed animals does not affect its life saving efficiency. This suggests that non-specific somatic mutations are insignificant in the failure of bone marrow to protect against the late life shortening effects of radiation; moreover, these somatic mutations are an unlikely cause of life shortening in the endogenous population of sublethally irradiated animals.

Lung Tumours. Correlative studies of the number of lung parenchymal cells exposed at a given age, and the late yield of different histological types of tumour in the lung, have shown that each lung tumour arises as an independent event. This has implications in the cumulative hazard of pulmonary cancer agents, and is of practical importance because of the relatively longer latent period of lung tumours. The observed decrease in yield of lung tumours at higher doses of radiation, or of a chemical carcinogen, may reflect the loss of potentially tumour cells from the population, due to the limited number of cell divisions of which the alveolar cell, for example, is capable. Such a model to explain the decreased tumour yield may be compared with the reported reduced yield of tumours in the liver, treated with a carcinogen, and repeatedly forced into cell division by partial hepatectomy.

The important differences in the behaviour of these two groups of tumours, the myeloid leukaemia and the pulmonary, if studied, may be very helpful in efforts to find a unifying mechanism for all cancer induction.

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PRECISION DOSIMETRY IN CLINICAL
RADIOLOGY

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RL 00099-18

Project Description and Objectives: There are two aspects of this research project. The first is to explore exhaustively the possible contributions of discipline of radiological physics in the field of patient exposure and image quality control in a busy Department of Radiology.

In the second area, the recent availability of solid state detectors with incredibly good energy resolutions made it feasible to explore the possible contribution of quantum spectrophotometry to the quantitative determination of impurities deposited in the lungs of industrial workers.

Significant Results: A master's thesis "Use of An Air Gap to Improve Contrast in Diagnostic Radiology," by Robert G. Gould was completed during the past year. A paper with the same title was presented by R. G. Gould and J. Hale at the Thirteenth Annual Meeting of the American Association of Physicists in Medicine (AAPM Quarterly Bulletin 5:106, 1971). The version of this work for publication is currently being prepared. An undergraduate student, R. L. Krigel, was awarded a Student Scholar Award by the Nuclear Science Group of the Institute of Electrical and Electronic Engineers on the basis of this Senior Honor's thesis "A Study of F Center Production in Pure Lithium Fluoride." A paper based on this work will be submitted for publication.

One paper is currently in press that was supported by this project. "The Use of Aluminum to Simulate Patient Attenuation in Diagnostic X-ray Beams" by R. G. Gould and J. Hale has been accepted by the Editor of *Acta Radiologica*.

In the area of quantum spectrophotography, a paper based on a master's thesis by W. Burch "Two Wavelength Techniques for the Measurement of Bone Mineral Content In Vivo" was presented by W. Burch and P. Bloch at the Bone Measurement Conference, May 22-23, 1970, in Chicago, Illinois. This paper was published in the Proceedings of the Conference. Two preliminary papers have been published by P. Bloch. "X-Ray Spectrophotometric Method Using a Silicon Lithium Drifted Detector for Determining In Vivo the Antimony Deposits in the Lung" appeared in *Radiology* 94:200, 1970. A short paper on the same subject "Gamma-Ray Spectrophotometric Method Using a Lithium Drifted Silicon Detector Determining In Vivo Antimony Deposits in a Lung" was published in *Radiology* 96:657-658, 1970.

Although the main thrust of this project is in the area of diagnostic radiology. Inevitably the investigator became involved in therapy dosimetry problems. P. Bloch published a paper "*In Vivo* Dosimetry with Extruded Lithium Fluoride Rods" in Radiology 96:425-427, 1970. A theoretical investigation of Californium-252 dosimetry "Calculation of the Dose Distribution about Californium-252 Needles in Tissue," by V. Krishnaswamy was partly supported by this project (Radiology 98:155-160, 1971). Additional experimental work was presented in a paper "Dose Distribution Around a Californium-252 Needle" by Krishnaswamy at the Thirteenth Annual Meeting of the AAPM (AAPM Quarterly Bulletin 5:111, 1971).

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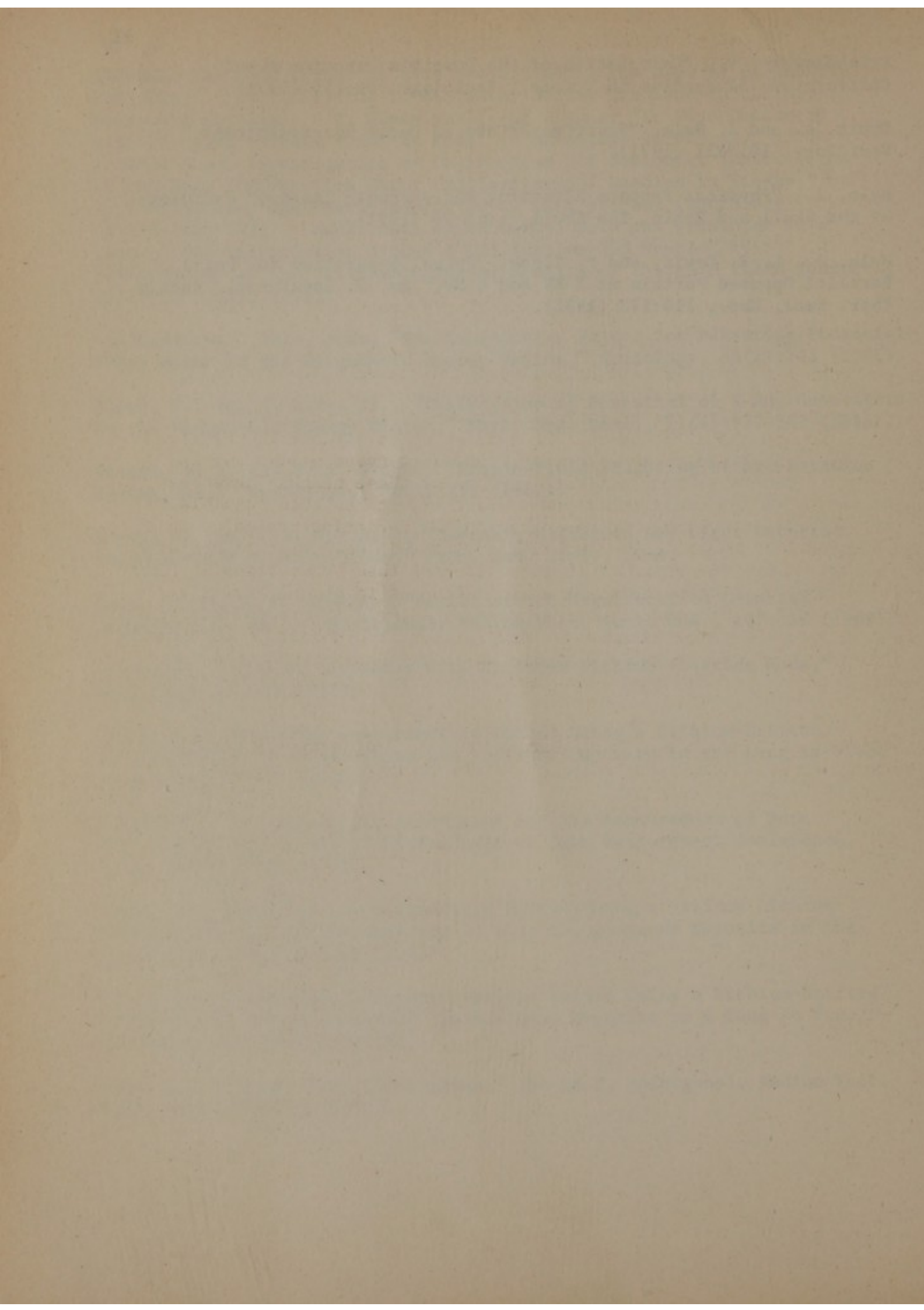
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RL-00104-04

Project Description and Objectives: To obtain information on the following questions:

1. Can low-level ionizing radiation have an effect on the central nervous system?
2. How is low-level ionizing radiation perceived by the mammalian central nervous system?

Significant Results: Investigations were undertaken to determine the structural and functional pathways by which mammals are able to perceive ionizing radiation in the ambient environment. Using the gerbil, *Meriones unguiculatus*, and x-radiation doses up to 3R/hour it was shown that ionizing radiation can effect the central nervous system and its functions. The total body activity rhythms of these mammals have been synchronized to the radiation regime. Further, it has been possible to alter the activity rhythms by manipulating the radiation regime to which the animals are exposed. The gerbil is relatively resistant to radiation (LD₅₀ dosage for the animal is 3 times greater than other rodents). However, in this radiation resistant animal, changes in normal activity rhythms have been observed by simply placing animals in a lead shielded room. Animals have been blinded, by enucleation, and do not demonstrate a significant change in their activity rhythms. However, changes were seen in normal activity rhythms caused by interruption of the olfactory pathways.

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1. The low-level ionizing radiation field in the atmosphere

2. The low-level ionizing radiation field in the atmosphere

3. The low-level ionizing radiation field in the atmosphere

4. The low-level ionizing radiation field in the atmosphere

RADIATION INDUCED CHROMOSOME
DAMAGE AND CELL RESPONSE

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RL 00401-01

Project Description and Objectives: To obtain information on the patho-physiologic processes involved in the production of somatic effects of ionizing radiation *in vivo*. Experiments are designed to simulate the temporal and physiologic conditions under which the effects of radiation develop. The parameters to be studied include the incidence and types of radiation-induced chromosomal lesions, the kinetics of cellular and tissue regenerative phenomena and the histopathologic response of the irradiated tissue. It is hoped that the data from this project, when correlated, will provide information that not only is presently unavailable, but that will provide a base on which additional information may be developed so that an appreciation may be gained of the mechanisms underlying the pathologic processes involved in the production of the somatic effects of radiation.

Significant Results: Significant progress is not available.

Publications: None.

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RADIATION INDUCED CHROMOSOME
DAMAGE AND CELL REPAIR

SI 00401-01

Abstract: To obtain information on the path-
physiologic processes involved in the production of somatic effects of
ionizing radiation in vivo. Experiments are designed to elucidate
the temporal and physiologic conditions under which the effects of
radiation develop. The parameters to be studied include the kinetics of
and types of radiation-induced chromosomal lesions, the kinetics of
cellular and tissue regenerative phenomena and the histopathologic responses
of the irradiated tissue. It is hoped that the data from this project,
when correlated, will provide information that not only is presently
unavailable, but that will provide a basis on which additional information
may be developed so that an appreciation can be gained of the mechanisms
underlying the pathologic processes involved in the production of the
somatic effects of radiation.

Keywords: Significant progress is not available.

Subject: None

EFFECTS OF RADIATION AND DRUGS
ON HAIR AND HAIR GROWTH

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RL 00580-01

Project Description and Objectives: Rapidly dividing hair cells will be used as a model system to study the biological effects of radiation alone or combined with drugs, duration of cellular injury and character of recovery. Results of dose fractionation, comparisons of different radiation modalities, and radiation effects on cell cycle kinetics will be investigated. Also electron microscope studies of ultrastructural changes characterizing radiation injury will be conducted.

Significant Results: The following principal studies were continued or completed in 1970 and 1971:

(1) Investigations in CF₁ mice were undertaken to study anagen matrix cell kinetics responses to ionizing radiation. Animals were treated with 100 rads at 45 kv 15 minutes after administration of tritiated thymidine (0.8 μ Ci/g). Individual follicles were dissected free from skin biopsy specimens and autoradiographs were prepared from follicle preparations. Mitotic indices were reduced within 30 minutes after x-ray exposure (2.4 percent in control vs. 1.8 percent in irradiated sites) and dropped sharply after two hours (2.2 percent vs. 0.7 percent). The mitotic index recovered to normal levels within 7 hours after irradiation. The post-radiation G₂ period delay was 1-1/2 to 2 hours. Studies of the 4 individual hair types revealed no significant differences in radiation responses.

(2) Studies of matrix cell kinetics in normal mouse hairs during the 19-day anagen (growing) period were continued. Cell cycle times of 11-12 hours were found to be constant in the different hair types at 2-3 day intervals from day 5 to day 16 of anagen. A 2-1/2 fold increase in labeled cells was noted from days 5-10 of anagen, following which no significant changes in matrix cell compartment sizes were noted. Telogen (period of mitotic inactivity) occurred from days 18-20 with abrupt termination of cell labeling and cell division. No lengthening of cell cycle times was found just prior to the onset of telogen. Cell population studies of matrix proliferative compartments revealed 2-1/2 fold differences in size from the smallest (zig-zag) to the largest (monotrich) hairs. Experiments with tritiated thymidine revealed that cell turnover times in proliferative compartments were rapid. Grain counts were halved in about 36 hours and the labeling index fell from 32 percent one hour after thymidine administration to 9 percent at the 78 hour interval. Following a single "flash" label with thymidine, replacement time of labeled S cells and their descendants was about 6 days.

(3) Experiments were undertaken to investigate the effects of hydroxyurea (HU) and radiation on hair matrix cells. HU 100 m/kg was administered intraperitoneally followed by tritiated thymidine 1/2 hour before biopsy up to 48 hours later. Follicle autoradiographs revealed a sharp drop in the mitotic index 30 minutes after drug administration (2.3 percent in controls vs. 1.5 percent in HU animals). Mitotic indices were 0.6 to 0.7 percent at 1-4 hours, returned to normal (2.5 percent) at 6 hours, and showed striking overshoot (3.2 - 4.0 percent) 8-10 hours after HU. Labeling indices were nil one hour after the drug, returned to normal (25 percent) at 4 hours, and showed an overshoot of (35 percent) at 5 to 6 hours. Ten hour peaks and troughs in mitotic and labeling indices suggested drug induction of a partially synchronous cell population. Nuclear necrosis and cell debris were most marked at 5-7 hours; recovery was almost complete 10 hours after drug injection. Proliferative cell compartments showed up to 50 percent reductions in cell populations.

After injection of HU 1200 m/kg the effects of varying the time intervals between drug and radiation (650 rads) from 1 to 12 hours were studied. Hair loss per square mm was measured four days later by photomicroscopy. Maximum alopecia (20 percent of hair "survival" occurring with radiation alone) was found at the 4 and 8 hour intervals, while relative "protection" against hair loss (80 percent of hair "survival" occurring with radiation alone) was found at the 6 hour interval.

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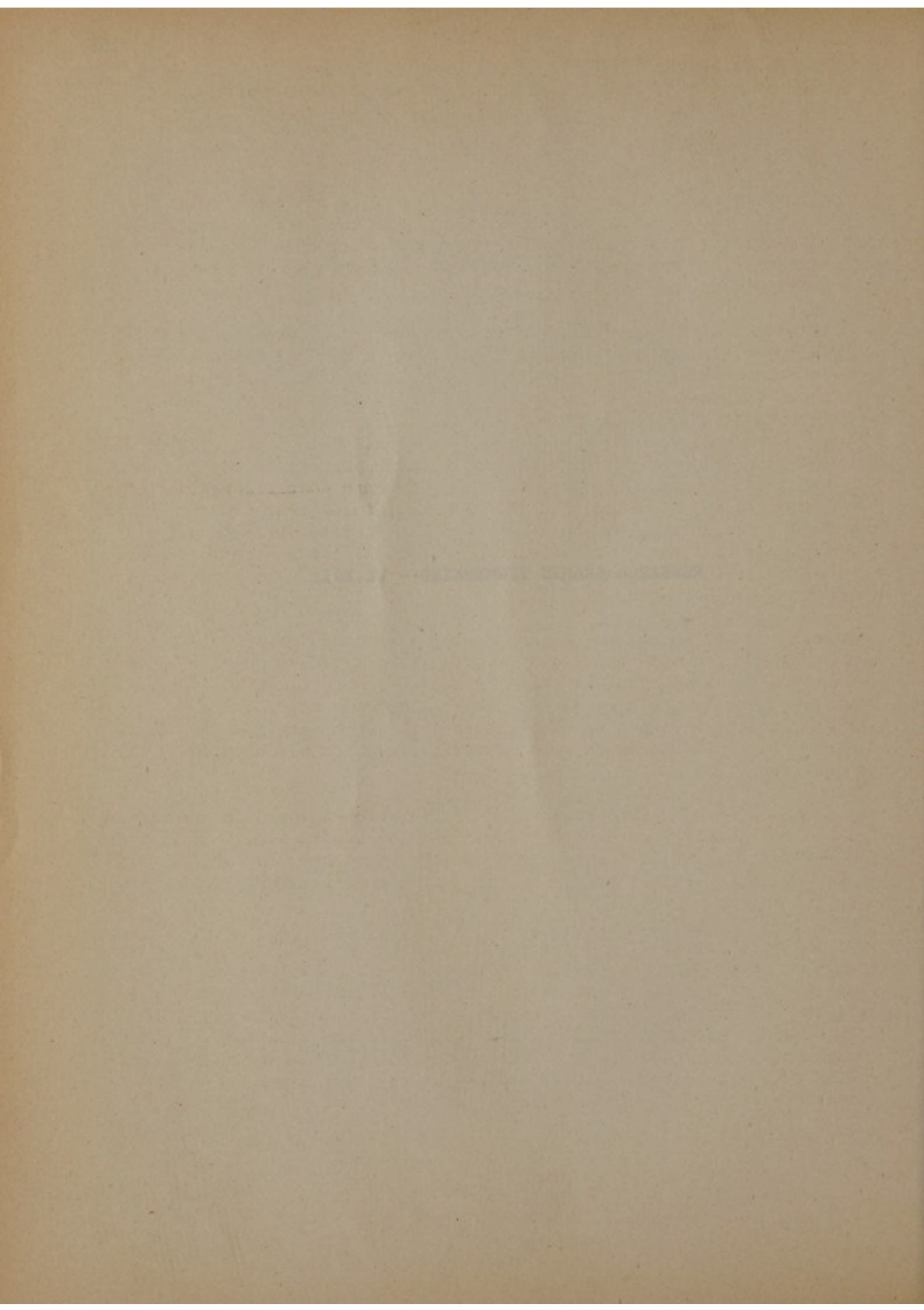
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RESEARCH GRANTS TERMINATED - FY 1971



THE EFFECTS OF X-IRRADIATION
OF THE SMALL INTESTINE

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EC-00066-14

Project Description and Objectives: The objective of this project is to learn more about the consequence of exposing the small intestine of rats to x-irradiation. Also to determine the sequence and quality of radiation-induced changes which precede the early loss of intestinal mucosa and in many cases the later appearance of intestinal tumors.

Significant Results: The study of radiation-induced intestinal carcinoma in rats has yielded the most significant results to date. The basic procedure involves delivering 2000 R of x-radiation to the temporarily exteriorized ileum and jejunum made ischemic by clamping the superior mesenteric artery and vein during 70 percent of the radiation exposure period. Holtzman, Simonsen, and August rats have been used. Intestinal carcinomata developed with high frequency in 50 percent of the Holtzman rats treated and were often seen in the 5-10 month postirradiation interval. Simonsen and August rats developed fewer intestinal tumors, 10 and 15 percent, respectively. The tumors were noted later (12-18 months) than in Holtzman rats and gut lesions besides carcinoma were seen, viz., angiosarcoma, fibrosarcoma, and osteogenic sarcoma. The reasons for the differences are being sought.

In Holtzman rats, resection of the tumor and restoration of intestinal continuity with an end-to-end anastomosis is followed by the development of additional tumors at other sites in the gut, and at a much faster rate than ever shown by the original lesion. This response presents an excellent opportunity to study tumor histogenesis. Accordingly, experiments to study the intestine which remains after resection of the primary tumor are underway.

The low incidence and late appearance of radiation-induced carcinoma in Simonsen and August rats plus the occurrence of other intestinal lesions is of great interest because the response is in marked contrast to that of the Holtzman strain. Therefore, some opportunities for establishing cause and effect exist.

Temporarily exteriorized segments (2.5 cm or 7.5 cm) of rat ileum were x-irradiated with 3000 R or 5000 R. Animals died between 10 and 200 days. A lesion characterized by extensive serosal fibrosis was produced in death of the animals was due to obstruction. There were no carcinomas or other tumors. Since humans accidentally and sometimes necessarily have segments of intestine irradiated during the course of therapy, it seems desirable to use additional combinations of segment length and x-ray exposure to determine which produce only ulceration, only tumors, or

damage which is almost entirely repaired after considerable time.

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COMPOUNDS TO PROMOTE EXCRETION OF RADIOISOTOPES

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EC-00069-08

Project Description and Objectives: Compounds are being developed to promote the excretion of radioisotopes. These preparations will find application in reducing the danger from radioactivity received by persons exposed to radionuclides. Thus, the hazards from nuclear accidents and bombs will be reduced, and long-lived radioisotopes may be used more safely for diagnosis and therapy in medicine. Organic complexes of a variety of elements are being synthesized and their properties studied.

Significant Results: A variety of compounds have been developed to promote the excretion of radioisotopes from the body. The compounds include preparations to remove radioactive cobalt, iron, manganese, mercury, and zinc; also compounds have been found to remove radionuclides of cesium, cobalt, and plutonium. All these preparations are still very much in the investigative stage as far as humans are concerned, but the animal work seems nearly complete.

Early in their work, it has been pointed out that the body burden of radionuclides can be determined easily by hair analysis. It was shown that the body burden of strontium-90 in rats showed good correlation with the hair content of this radioisotope. They and others have shown that this same principle applies to dogs and man, not only for strontium-90, but for many radioelements. The concept of using hair as an index of the level of a toxic element had previously been applied to arsenic, and is currently being used extensively to diagnose exposure to cadmium, lead, and mercury.

Another important discovery is being evaluated in other programs. It was found that radio-zinc was accumulated in the arteries of experimental animals. The accumulation was especially high if the animals were zinc deficient. The retention suggested that zinc is important to the maintenance and repair of blood vessels. Since zinc deficiency has also been found to be common in patients with atherosclerosis, an inexpensive therapy has been introduced for the treatment of inoperable vascular disease. This therapy consists of oral medication of a zinc deficient patient with zinc sulfate capsules, 220 mg t.i.d. The results have been gratifying in patients suffering from intermittent claudication, but it will be some years before the merits of the therapy can be evaluated. It is suspected that zinc therapy promotes repair of the arteries just as it has been found to accelerate healing of burns and wounds. Thus, the medication introduced for external healing may have great utility for internal repair.

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RADIOBIOLOGICAL RESEARCH ON
MARINE ORGANISMS

H. Burr Steinbach
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Woods Hole, Massachusetts

EC-00071-11

Project Description and Objectives: This grant supports a hot lab area, comprised of ten inter-connecting rooms, on the fourth floor of Whitman Laboratory, at the Woods Hole Marine Biological Laboratory. These rooms, equipped with appropriate counting devices as well as radiation sources, are made available to qualified investigators. The funds also defray the expenses of the radiation safety officer and his assistant.

Significant Results: Since this grant relates to a wide variety of radiobiological experiments it is only possible to indicate results from a few of the many researches that have benefited from this support.

Results of research on mitotic delay in the eggs of the sea urchin *Arbacea Punctulata* have shown that treatment with high hydrostatic pressure and potential-parthenogenic activating agents leads to a reduction of radiation-induced mitotic delay. It is thought that this delay may be due to either initiation of events which permit the cell to bypass the stages normally delayed by radiation or to stimulation of repair mechanisms.

Studies of the effects of Cesium-137 gamma-rays on regeneration in the coelenterate *Tubularia* has yielded data related to radiation dose response, for regeneration can be increasingly protracted and the process completely inhibited. The lethal dose for the organism is in the range required to deactivate many viruses.

The radiation sensitivity of Sorcoma-180 and Krebs-2 in white albino mice was shown to be markedly increased in mice treated with keto-aldehydes and irradiated with Cesium-137 gamma rays.

A wide variety of experiments involved the use of radioactive tracers in studies of fundamental biological mechanisms including nerve conduction, active membrane transport, bioluminescence, differentiation, and bioregulation.

Publications: None.

Dr. Paul Steinberg
Marine Biological Laboratory
Woods Hole, Massachusetts

IONIZING RADIATION RESEARCH ON
MARINE ORGANISMS

000000-11

These investigations and observations. This grant supports a hot lab area, located on the interconnecting rooms, on the fourth floor of the main building, at the Woods Hole Marine Biological Laboratory. These areas, equipped with appropriate counting devices as well as radiation sources, are available to qualified investigators. The funds also cover the expenses of the radiation safety officer and his assistant.

Qualifications: Since this grant relates to a wide variety of biological experiments it is only possible to indicate results from few of the many researches that have benefited from this support.

Results of research on effects of radiation on the eggs of the sea urchin, *Strongylocentrotus purpuratus*, have shown that treatment with high hydrostatic pressure and potential-particulate activity agents leads to a reduction in radiation-induced mitotic delay. It is thought that this delay may be due to either inhibition of events which precede the cell to bypass the stages normally delayed by radiation or to stimulation of repair mechanisms.

Studies of the effects of Gamma-137 gamma-rays on regeneration in the planarian *Dugesia* have yielded data related to radiation dose response, for regeneration can be increasingly restricted and the process completely inhibited. The lethal dose for the organism is in the range required to deactivate many viruses.

In radiation sensitivity of *Sarcosine-135* and *Krebs-2* in white albino mice was shown to be markedly increased in mice treated with hydroxybenzyl and irradiated with Gamma-137 gamma rays.

A wide variety of experiments involving the use of radioactive tracers in studies of fundamental biological mechanisms including nerve conduction, active membrane transport, photosynthesis, differentiation, and photoreception.

References: None.

INACTIVATION OF ENZYMES BY IONIZING RADIATION

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EC-00072-11

Project Description and Objectives: To inquire into the basic mechanisms of radiation effects by studying the irradiation of ribonuclease, one of the enzymes which may be involved in the control of growth and reproduction. It is hoped to obtain a sophisticated understanding of how irradiation damages the enzyme molecule, and how such damages correlate with impairment of enzyme function.

Significant Results: Evidence of striking similarities between gamma-irradiated ribonuclease and samples obtained by treatment of this enzyme with chemically produced hydroxyl-radicals (from Ferrous and Peroxide), was revealed in earlier work. Subsequent studies showed that irradiated enzyme was extensively "unfolded," and led to a re-examination of hydroxyl treated enzyme, with a view towards comparing its structure with that of irradiated enzyme. The aim of continued studies was to evaluate hydroxyl treatment as a model of the irradiation effect.

A further similarity was reported between the irradiated and hydroxyl treated ribonuclease: Unlike native enzyme, both types of inactivated samples complexed strongly to ferric and ferrous iron. The iron-protein complexes were isolated from reaction mixtures by gel-chromatography; specific color tests measured ferrous and ferric iron.

Continued studies have demonstrated the accuracy of the iron color tests. When radioactive iron was used in experiments, color estimates of total iron agreed well with values obtained by isotope assay. As much as four atoms of total iron have been found complexed to an inactivated protein; this probably being a minimum value, since the gel is a strong competitor for ferric ions. Irradiated enzymes bind more to added ferric than added ferrous. Color tests show hydroxyl inactivated protein contains both ferric and ferrous ions; the proportion of ferrous ions increases markedly with time. Irradiated enzyme-ferric complexes similarly show conversion of ferric to ferrous on standing. Thus, both types of inactivated protein iron complexes behave like redox metal proteins.

Iron complexing to irradiated ribonuclease occurs even weeks post-irradiation, and is obviously related to the permanently unfolded state of the molecule. The same considerations may apply to hydroxyl inactivated enzyme. (Prototypes unfold molecules, such as oxidased ribonuclease and heat-denatured enzyme, did not bind iron. Reduced enzymes reduced ferric ions, but the recovered protein contained only a trivial amount of ferrous ions.)

Both irradiated and hydroxyl treated enzyme-iron complexes are isolated in weak acidic, to, or almost, neutral media, in which the complexes are very stable. In strong acid the complexes are very stable. In strong acid the complexes disassociate to yield iron-free proteins, which can be isolated and studied. This method is being used to purify hydroxyl treated enzymes from complexed iron, (which separates on gel-chromography as an iron-complex), so that the physical-chemical properties of the protein product can be compared with those of irradiated enzyme.

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ENZYMATIC AND ESR STUDIES OF
RADIATION DAMAGE

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EC-00073-10

Project Description and Objectives: To increase understanding of how radiation-induced chemical processes occur in cells and how they can be modified. In order to elucidate the fundamental mechanisms responsible for biological radiation damage and repair, important biomolecules are irradiated, individually and in combination with modifying substances, and the radiation changes are followed with chemical and physical methods. The results are used to interpret experiments carried out on simple biological systems such as bacteria and red blood cells.

Significant Results: Work on the mechanism of transfer of unpaired spins from macromolecules to sulfur compounds has been continued. Recently it was found that in oxidized penicillamine, sulfur resonance can be detected immediately after irradiation at 77°K. By utilizing this observation it was possible to establish that in certain mixtures of macromolecules with penicillamine an extensive transfer of spin occurs already at 77°K. Previous electron spin resonance studies of the indirect effect in frozen aqueous solutions and suspensions have been continued using different charged derivatives of cross-linked dextran. The results show that the extent of the indirect action is the same for uncharged and negatively charged derivatives, while it is significantly larger for positively charged derivatives. The results indicate that excited water molecules may partly be involved in the indirect action observed at low temperatures in the frozen state.

The x-ray inactivation of an enzyme having two different functions, viz. the threonine-sensitive asparto-kinase homoserine dehydrogenase from *E. coli*, has been studied. The results indicated that one of the functions was preferentially destroyed. Thus, the kinase activity of the enzyme was two to three times as sensitive as the dehydrogenase function. The results suggested that the loss of the kinase function was caused by destruction of sulphydryl groups involved in the maintenance of the enzyme complex.

It is believed that the results obtained have contributed to the knowledge of the mechanism whereby DNA, enzymes and proteins are inactivated by irradiation, and how, under certain conditions, the damage can be prevented or repaired. Such knowledge is considered essential as a basis for developing improved procedures for therapeutic application of ionizing radiation and for protective procedures against undesired irradiation. The inactivation studies of enzymes are of importance with regard to radiation sterilization of enzymes used in the food industry.

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LOCAL CHEMICAL RADIATION
PROTECTION IN MICE

Robert A. Goepp
University of Chicago
Chicago, Illinois

EC-00081-06

Project Description and Objectives: To determine the degree and character of radiation protection afforded by different chemical agents applied directly to the mouse tongue. The chemical agents that will be used are mercaptoethylamine, (MEA), aminoethylisothuromium, (AET), and para-aminopropiophenone, (PAPP). The assessment of protection will be determined by the ability of these chemicals to alter the mortality of oral radiation death and their ability to prevent or alter the sequence of histologic changes in the irradiated tongue which precede death. In particular the degree of protection afforded by the radiation protection chemicals will be measured by comparison of DNA synthesis and mitosis rates between protected and nonprotected irradiated epithelium.

Significant Results: It has been found that mercaptoethylamine afforded the best degree of protection (DRF, 1.35) as measured in the mortality studies. Para-aminopropiophenone afforded very little protection when applied locally. Preliminary review of the cell population kinetics data suggests a far higher degree of protection than that seen in mortality studies. Mortality studies are a more indirect, remote measure of topical chemical radiation protection. The kinetics data is presently being studied in statistical analysis.

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EEG AND BEHAVIORAL EFFECTS OF
GAMMA RADIATIONS

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EC-00090-03

Project Descriptions and Objectives: To develop a clearly defined index of electrical activity which can be followed at different levels of the brain--peripheral, subcortical, and cortical, and to investigate effects of irradiation on the nervous system. Other objectives are concerned with establishing relationships of behavioral effects to irradiation.

Significant Results: The research has focused on the comparative effects of whole body and head only irradiation in cats. With groups of head only irradiation from 800 to 1200 R, there were no consistent effects on the power spectral analysis of the EEG and performance in a visual discrimination task. With whole body irradiation at 500 R there were consistent differences in electricity from olfactory bulbs and limbic structures at 3 and 24 hours post, a return to pre-irradiation by 72 hours, and a change again in electricity and also behavior at from 7 through 14 to 17 days when death ensued.

With head only irradiation at 500 to 1000 R, there were no changes either in the analyses of the EEG or behavioral performance immediately after irradiation and up to 90 days post. With head only irradiation at 2000 to 3000 R, the same changes in brain EEG and behavior were observed as with whole body irradiation--a change in the electrical activity with no deficit in behavior at 3 to 24 hours; a return to the preirradiation EEG at 72 hours, and a change again in the electricity with behavioral deficit at 7 through 20 days when death ensued.

There were the same reversible EEG effects with both 500 R whole body and 2000 to 3000 R head only irradiation, which appeared to implicate chemical mediation through the blood system. This was confirmed by relations between the successive electrical changes and brain serotonin levels in both the whole body and head only irradiation groups. There also appeared to be a time-dependent effect of up to 7 days post-irradiation on the behavioral measures for both the whole body and head only irradiation groups which requires further analysis.

Publications: None.

David E. Miller
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EKG AND BEHAVIORAL EFFECTS OF
GAMMA RADIATION

EC-00000-01

Project description and objectives: To develop a series of tests of electrical activity which can be followed at different levels of the brain--cortical, subcortical, and cortical, and to investigate effects of irradiation on the nervous system. Other objectives are concerned with establishing relationships of behavioral effects to irradiation.

Summary of results: The research has focused on the comparative effects of whole body and head only irradiation in rats. With groups of head only irradiation from 500 to 1500 R, there were no consistent effects on the power spectral analysis of the EEG and performance in a visual discrimination task. With whole body irradiation at 500 R there were consistent differences in electrical activity from olfactory bulbs and limbic structures at 3 and 14 hours post-irradiation. A return to pre-irradiation levels of change again in electrical activity and also behavior at 14 through 16 to 17 days when death ensued.

With head only irradiation at 500 to 1000 R, there were no changes either in the analysis of the EEG or behavioral performance immediately after irradiation and up to 70 days post-irradiation. With head only irradiation at 1000 to 3000 R, the same changes in brain EEG and behavior were observed as with whole body irradiation--a change in the electrical activity with no deficit in behavior at 3 to 14 hours; a return to the pre-irradiation EEG at 12 hours, and a change again in the electrical activity with behavioral deficit at 7 through 10 days when death ensued.

There were the same reversible EEG effects with both 500 R whole body and 1000 to 3000 R head only irradiation, which appeared to implicate chemical mediation through the blood system. This was confirmed by relations between the successive electrical changes and brain serotonin levels in both the whole body and head only irradiation groups. There also appeared to be a time-dependent effect of up to 7 days post-irradiation on the behavioral measures for both the whole body and head only irradiation groups which requires further analysis.

References: None.

EFFECT OF RADIATION ON PROTEINS
AND RELATED COMPOUNDS

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EC-00091-06

Project Descriptions and Objectives: To investigate how free radicals interact with biological materials and to investigate the mechanisms of such interactions.

Significant Results: The effect of radiation on amino acids and proteins has been extended by studying the effects of ultraviolet light on a series of L-tyrosines and their polymers. A number of products have been obtained from among the irradiated samples and these are being identified.

Collagen samples have been obtained from genetically homogeneous mice of different age groups and from mice which have been exposed to ionizing radiation. The collagen samples were obtained from the skins of mice and separated into "neutral salt soluble," "acid soluble" and "insoluble" fractions. The properties of these fractions have been investigated, using a number of different techniques including amino acid analysis, solubility and behavior on starch gel electrophoresis. The aim of this work is to investigate in which sense the effects of age and of radiation are similar.

The radicals obtained on heating 3,4-benzpyrene have been further investigated and a new radical has been identified in the presence of air. The radical is a phenoxy radical and is very readily formed in the presence of biological materials from 3,4 benzpyrene. It is also obtained from 5-hydroxy-3,4-benzpyrene in good yield and this aids in its identification. Somewhat surprisingly, the latter compound, which readily gives rise to the phenoxy radical, is biologically inactive, although 3,4-benzpyrene is a potent carcinogen. The reason for this is being investigated.

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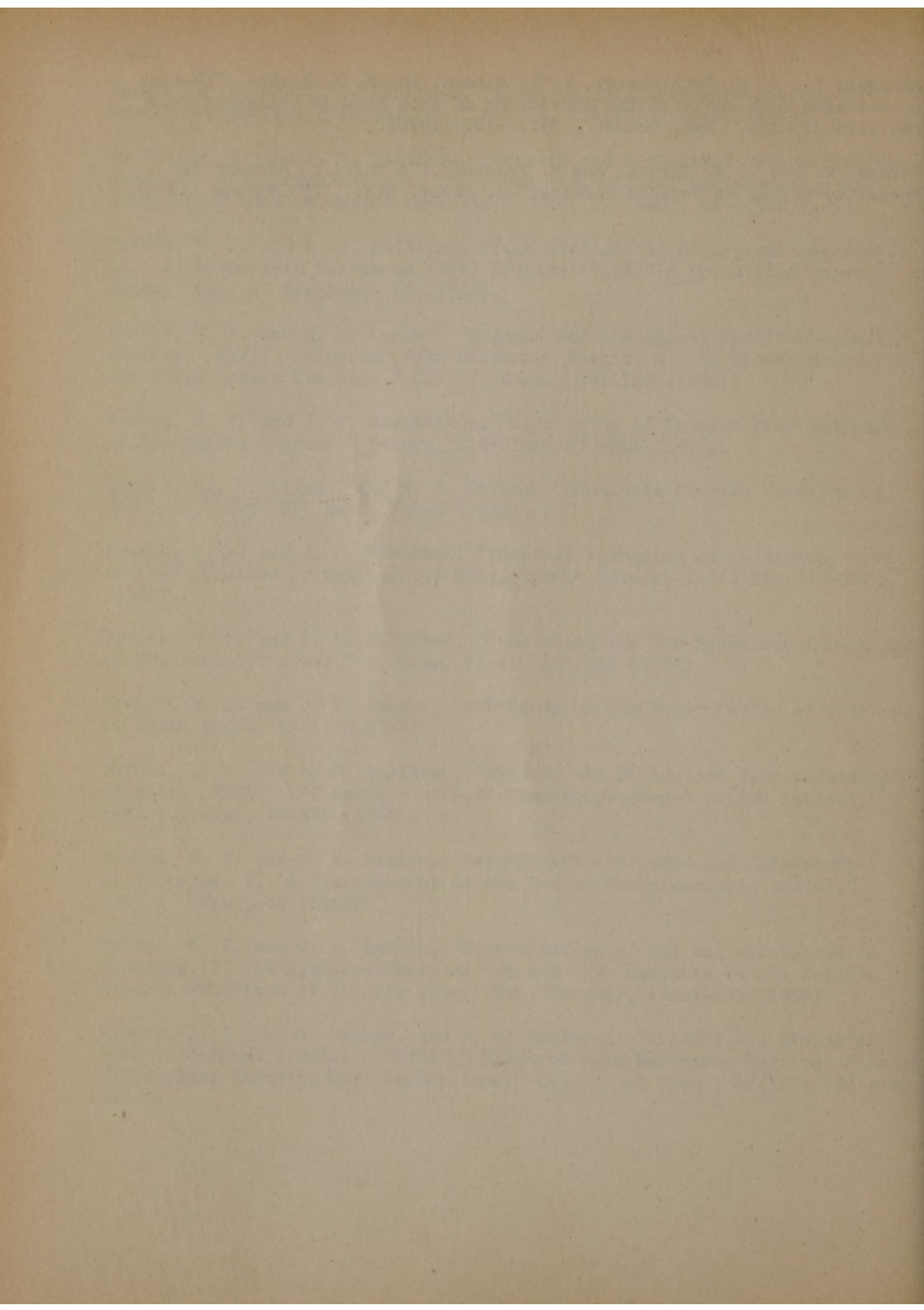
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RADIATION STUDIES IN IONIC MATRICES

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University Park, Pennsylvania

EC-00097-03

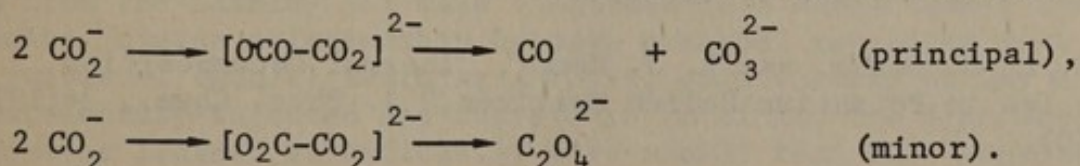
Project Description and Objectives: Simple inorganic and organic ions, which are present in biological systems or which can serve as chemical models of more complex biological compounds, are dispersed in solid potassium halide matrices, and these solids are exposed to ionizing radiations. The chemical changes of the solute ions produced in these samples will be characterized by measuring the infrared, ultraviolet, visible, and/or electron paramagnetic resonance spectra of the samples.

Significant Results: The carbon dioxide anion free radical (CO_2^-) and the carbonate anion free radical (CO_3^-) are produced during the radiation damage of carbonates, biocarbonates, or carboxylates. These very reactive free radicals have been trapped in potassium chloride (KCl) and potassium bromide (KBr) matrices in sufficient concentrations and studies have been made of some of their important chemical reactions.

The CO_2^- radical reacts rapidly with water and produces the formate (HCO_2^-) and the bicarbonate (HOCO_2^-) ions. However, in the absence of water, this free radical decays by a bimolecular process and gives only diamagnetic products. The decay reaction rate constants in KCl and KBr matrices are respectively:

$$\begin{array}{lll} 10^{9.37 \pm 0.10} & \exp[(-18.93 \pm 0.20 \text{ kcal})/RT] & \text{liter/mole-second,} \\ 10^{6.59 \pm 0.08} & \exp[(-11.89 \pm 0.15 \text{ kcal})/RT] & \text{liter/mole-second.} \end{array}$$

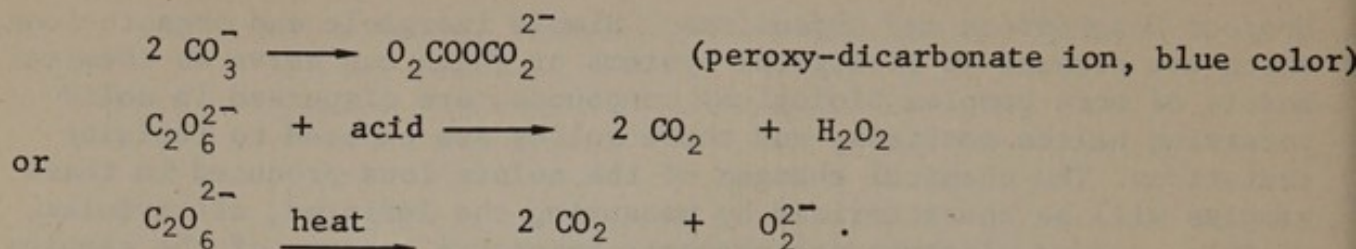
The principal reaction products in both matrices are the carbon monoxide gas (CO) and the carbonate ion (CO_3^{2-}), but some oxalate ions ($\text{C}_2\text{O}_4^{2-}$) are also produced in the KCl matrix. Thus, the reaction mechanism for the decay of this radical in the absence of water is as follows:



The CO_3^- free radical does not appear to react with water, but its decay in KCl and KBr matrices is also bimolecular. The experimental decay rate constants for the respective matrices are:

$$\begin{array}{lll} 10^{14.8 \pm 0.8} & \exp[(-10.3 \pm 0.4 \text{ kcal})/RT] & \text{liter/mole-second,} \\ 10^{11.9 \pm 0.8} & \exp[(-9.6 \pm 0.5 \text{ kcal})/RT] & \text{liter/mole-second.} \end{array}$$

The decay product or products are diamagnetic, relatively stable thermally, and show a blue color. Dissolution of the reaction system in acidified water gives a positive test for peroxide. The known peroxy-dicarbonate ion ($C_2O_6^{2-}$) exhibits these properties, and it is suggested that the decay mechanism of our CO_3^- free radical is as follows:



Since the CO_2^- and CO_3^- free radicals are iso-electronic (same number of electrons in the molecules) with the well known free radicals NO_2 and NO_3 , respectively, much of the chemistry of our anion radicals can be understood from the known behavior of the nitrogen oxide radicals.

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CYSTEAMINE AND X-RAYS PRENATALLY:
BEHAVIOR OF THE RAT

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EC-00106-05

Project Description and Objectives: To further study the effects on the mental and emotional functioning of offspring whose mothers were exposed to ionizing radiation during pregnancy. Studies with the drug, cysteamine, that have been shown to protect these offspring against the central nervous system damage that often follows radiation exposure are also conducted.

Significant Results: It has been shown that cysteamine (100 mg/kg of body weight) given to the pregnant animal prior to irradiation is protective against neonatal death, motor retardation, and learning deficiencies in the offspring. This was observed following exposure to 110 R or 185 R of gamma-radiation. Cysteamine injected subcutaneously was also investigated to determine whether this route of administration would produce as protective an effect as the intraperitoneal method. Since cysteamine at the dosage given above (low dose) was found ineffective when given after irradiation, another group was given twice the cysteamine dosage (200 mg/kg) immediately following irradiation. The days of pregnancy studied were Day 15 and Day 20 (gestation period of the rat is 22 days).

On two tests of motor development, the upright and the righting response, neonates who received 185 R prenatally developed more slowly than the controls. This was more marked in the groups irradiated on Day 15 on both motor development measures. Those receiving the low cysteamine dose developed earlier than the other groups including the "unprotected" controls (no cysteamine, no irradiation). Cysteamine injected as a control (no irradiation) slowed development slightly but not the extent seen in the high cysteamine dose group. The high cysteamine groups were remarkably slowed in development even in comparison with the high radiation dose group (185 R) that received no cysteamine. The most retarded of the groups was the subcutaneously-injected high cysteamine group.

Data from the Lashley III maze (modified to a water maze), showed a definite inverse relationship between prenatal radiation dose level and postnatal (adult) learning ability, particularly on Day 15. The subcutaneously-injected and the groups receiving the high dose of cysteamine learned significantly more slowly than the "unprotected" high radiation groups. This was seen in both male and female offspring indicating no sex difference in response to cysteamine prior to prenatal irradiation. Marked deficiencies in learning ability were found when cysteamine was given subcutaneously. The cysteamine-after-irradiation groups were also greatly impaired in their learning ability. On Day 20, no protection was offered. However, these animals made fewer errors in learning to traverse the maze than those animals receiving the same

dose of radiation (185 R) on Day 15. Differences in the stage of fetal brain development undoubtedly account for this finding.

Publications: Roberts, J. M., "Cysteamine Protection Against Lethal and Growth-Inhibiting Effects of Prenatal X and Gamma Irradiation," *Teratology*, 3(4):319-324 (1970).

Roberts, J. M., "Prenatal Chemical Protection Against Radiation-Induced Learning Deficiencies," *Rad. Res.*, 49(2):311-321 (1972).

BIOCHEMICAL CHANGES IN SKIN
INDUCED BY IRRADIATION

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EC-00110-03

Project Description and Objectives: A systematic investigation into the biochemical alterations produced by sunlight and ultraviolet light irradiation on human intact skin is to be conducted. In particular, careful attention will be given to biochemical modifications which may give some clue to the mechanisms *in re*.

1. The capacity of irradiation and environmental factors to injure skin with the ensuing production of erythema, inflammatory response, promotion of pigment formation, acceleration of degenerative changes and of premature aging.

2. The relationship of ultraviolet light to photosensitivity and its role in precipitating or aggravating systemic diseases such as lupus erythematosus, pellagra, porphyria and photosensitization phenomenon associated with certain drugs.

3. The influence of sunlight and ultraviolet light on enzyme activity and the formation of substances with potent biochemical and physiological actions both beneficial (e.g., formation of Vitamin D) and deleterious (e.g., formation of pre-malignant and malignant skin morphology).

It is hoped that this investigation will contribute to a better understanding of photobiology.

Significant Results: The most significant finding is that exposure of the skin to sunlight or broad spectrum ultraviolet light brings about a profound reduction in the content and rate of formation of new fat, particularly cholesterol. This may be important; under some circumstances, the skin contributes significantly to the levels of cholesterol related sterols and lipids in the blood and other tissues.

Though not generally realized, it may be possible to lower blood cholesterol and other lipid pools by exposing the skin to sunlight. The amount of exposure to sunlight may be a mixture of good and evil to man. Moderate amount of sunlight is essential for the production of Vitamin D by the skin and may control levels of fat in the blood; excessive exposure to sunlight predisposes man to skin cancer and precocious aging. Work is now in progress to help elucidate and extend knowledge how ultraviolet light affects the biochemistry and physiology of skin.

Publications: None.

CANCER THERAPY BY INTERSTITIAL AND INTRACAVITARY RADIATION

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RL-00113-03

Project Description and Objectives: Interstitial and intracavitary radiation are of great importance in cancer management and there is no new modality in prospect which promises to replace either of them in the treatment of cancer. However, despite the generally accepted usefulness of interstitial and intracavitary radiation, there is considerable reluctance of most clinicians to use these techniques because of the radiation exposure problem.

In order to significantly decrease radiation exposure and at the same time achieve more effective interstitial and intracavitary radiation therapy, the development of new isotope sources and techniques is proposed. For interstitial radiation therapy the use of low energy seeds is proposed as a substitute for presently used high intensity radioisotopes. For intracavitary radiation therapy the use of "remote after-loading" with small high intensity sources moving during treatment is outlined. This technique promises to eliminate all radiation exposure to administering personnel and make intracavitary radiation as safe and simple as x-ray therapy. The major effort during this investigation will be placed on the problem of dosimetry and radiation exposure. Clinical evaluation of the beneficial effects as well as the side reactions of interstitial and intracavitary techniques and the radioisotopes involved will be carried out.

Significant Results: Economic production of iodine seeds for permanent implantation became possible largely because of automation and increased production of the seeds by the manufacturers. The cost was thus brought down to \$5.00 a seed, instead of \$12.50 a seed, which was the cost at the initiation of this project. No other isotopes were investigated however for permanent implantation because of the prohibitive cost of production (e.g., Cs-131 seeds are in the order of \$50.00 per seed). Because of the ready availability of the iodine seeds and their acceptance by the clinical services at Memorial Hospital, they were adopted as the only radioactive sources for permanent implantation at Memorial Hospital since September, 1969. The design of a special source inserter (gun) with a suitable magazine for inserting low energy sources has improved and simplified the technique of permanent interstitial implantation. The use of I-125 seeds and the clinical application of remote afterloading for some of the intracavitary applications has brought a dramatic reduction in radiation exposure to the extent that the exposure recorded on the personnel film badges is negligible, in contrast to earlier years when Rn-222, Au-198, Ir-192 and Ra-226 were used. Extensive studies on seed

calibration localization and dose distribution were conducted by the Medical Physics Department. Methods of dosimetry were developed which are adequate for using the I-125 seeds in clinical applications. Determining the proper dose with iodine seeds presented a problem for some time but was satisfactorily solved by associating the dose to the implanted volume, and referring to the previous experience with high energy gamma emitters. In intracavitary radiation, the Remote After loader was put into clinical use during the period of Grant RL 00113-03. New intracavitary applicators were designed and constructed for cancer of the nasopharynx, endometrium, and intraoral lesions and several technical refinements were achieved. An atlas of isodose distributions was prepared for different source excursions.

Clinical Studies: From May 1 to April 30 a total of 234 implants with I-125 seeds were performed in 221 patients. Permanent interstitial implants with I-125 seeds proved to be of particular value in cancer of the lung and prostate. In addition, 402 intracavitary applications were performed in 196 patients during the same period.

Publications: Hilaris, B. S., "Surgical Radioisotope Therapy," Residents Manual, Memorial Hospital for Cancer and Allied Diseases (1968-1969).

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Martini, N., B. S. Hilaris and E. J. Beattie, Jr., "Interstitial vs. External Irradiation Combined with Pulmonary Resection in Lung Cancer," Cancer, 26(3):638-641 (1970).

Hilaris, B. S., R. K. Luomanen, G. D. Mahan, and U. K. Henschke, "Interstitial Irradiation of Apical Lung Cancer," Radiology 99(3):655-660 (1971).

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Evans, S. R., Jr., B. S. Hilaris, and H. R. K. Barber, "External vs. Interstitial Irradiation in Unresectable Recurrent Cancer of the Cervix," Cancer, 28(5):1284-1288 (1971).

MERCAPTOCYCLOPROPYLAMINES:
RADIATION-PROTECTION AGENTS

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EC-00115-04

Project Description and Objectives: A review of the literature suggests that chemical modification of the mercaptoethylamine structure continues to be worthwhile in the synthesis of new radioprotective agents; some highly active derivatives have been reported. This project concerns the synthesis and biological evaluation of structurally rigid compounds which represent molecular modifications of mercaptoethylamine and mercaptopropylamine.

These two compounds are among the most potent radioprotective agents and a study of compounds in which the NH_2 and SH groups are *cis* (i.e. held on the same side of the molecule) or *trans* (held on opposite sides of the molecule) should be complementary to the work of others concerning *in vivo* mechanism of action. For preparation and biological evaluation of such *cis* and *trans* isomers (compounds with the same formula, but different geometry of substituents) a cyclopropane ring system is desirable. Utilization of the 3-membered ring represents the smallest function for importing rigidity to the molecule and therefore enables synthesis of the *cis* and *trans* isomers most closely related to the parent mercaptoalkylamines.

Significant Results: Two very important radiation-protective agents are beta-mercaptoethylamine (MEA) and gamma-mercaptopropylamine (MPA). During the past year, a study has been made of preparation of compounds (mercaptocyclopropylamines) related to MEA and MPA. These compounds have rigid structures and will be employed in the study of structural requirements for radiation-protective activity in animals. Studies on the chemistry of these unknown compounds have resulted in two publications. The thesis summarizes much of the work to date relative to the titled compounds. Two compounds have been submitted for biological evaluation. The Division of Medicinal Chemistry, Walter Reed Army Hospital, will evaluate these compounds in mice for radiation-protective activity; they will be assayed against normally lethal doses of ionizing radiation.

It is anticipated that the biological results will be of primary significance and will aid in directing future research in small ring mercapto-amine radiation-protective chemistry. The results should be of significance in elucidating the mechanism of action of these very important *in vivo* protectors against ionizing radiation. In the future, information obtained from these studies should be of value in studying radiation-damage and protection in humans. Presently, the synthetic chemistry which has evolved is also of significance and will be of value to a number of chemists working in related areas.

Successful synthesis of an acid unstable derivative of mercaptocyclopropylmethylamine represents one of the major accomplishments during the past year. This compound is a rigid compound related to MPA. It is anticipated that the compound, which has been separated into the pure *cis* and *trans* isomers, will show significant radiation protective activity. Also it is expected that there will be a difference in potency depending upon whether the groups on the cyclopropane ring are *cis* or *trans*. Biological results obtained will be of major importance for the direction of future research. These results should be forthcoming within the next three or four months. Study is being continued to explore the chemistry of these, as well as a number of related small ring analogs of MEA and MPA.

The synthesis of such small ring compounds requires the development of new reaction pathways and separation and purification techniques. Success has been made in developing a number of important synthetic routes in this area; a variety of physical methods have been worked out for the purification of the synthesized compounds in order that the pure compound may be submitted for biological evaluation. Particularly difficult was separation of pure *cis* and *trans* isomers. Methods have been developed for their separation, purification and structural identification. Research papers are being written on some of these results for publication in major chemical and biological journals.

Publications: Witiak, D. T. and M. E. Lu, "Product Ratio Analysis of the Reaction of Methyl *cis*- and *trans*- β -(Acetylthio) acrylates with Diazomethane," J. Org. Chem., 33(12):4451-4454 (1968).

Witiak, D. T. and B. K. Sinha, "Pyrazole Product Ratio Analysis of the Reaction of Diazomethane with Methyl *cis*- and *trans*- β -Chloroacrylates," J. Org. Chem., 35(2):501-503 (1970).

Witiak, D. T., and M. E. Lu, "Synthesis of *cis*- and *trans*-2-(2'-Tetrahydropyranyltio)cyclopropylmethylamines," J. Org. Chem., 35(12):4209-4217 (1970).

IN SITU ASSAY OF RADIOACTIVITY
FOR DOSE CALCULATIONS

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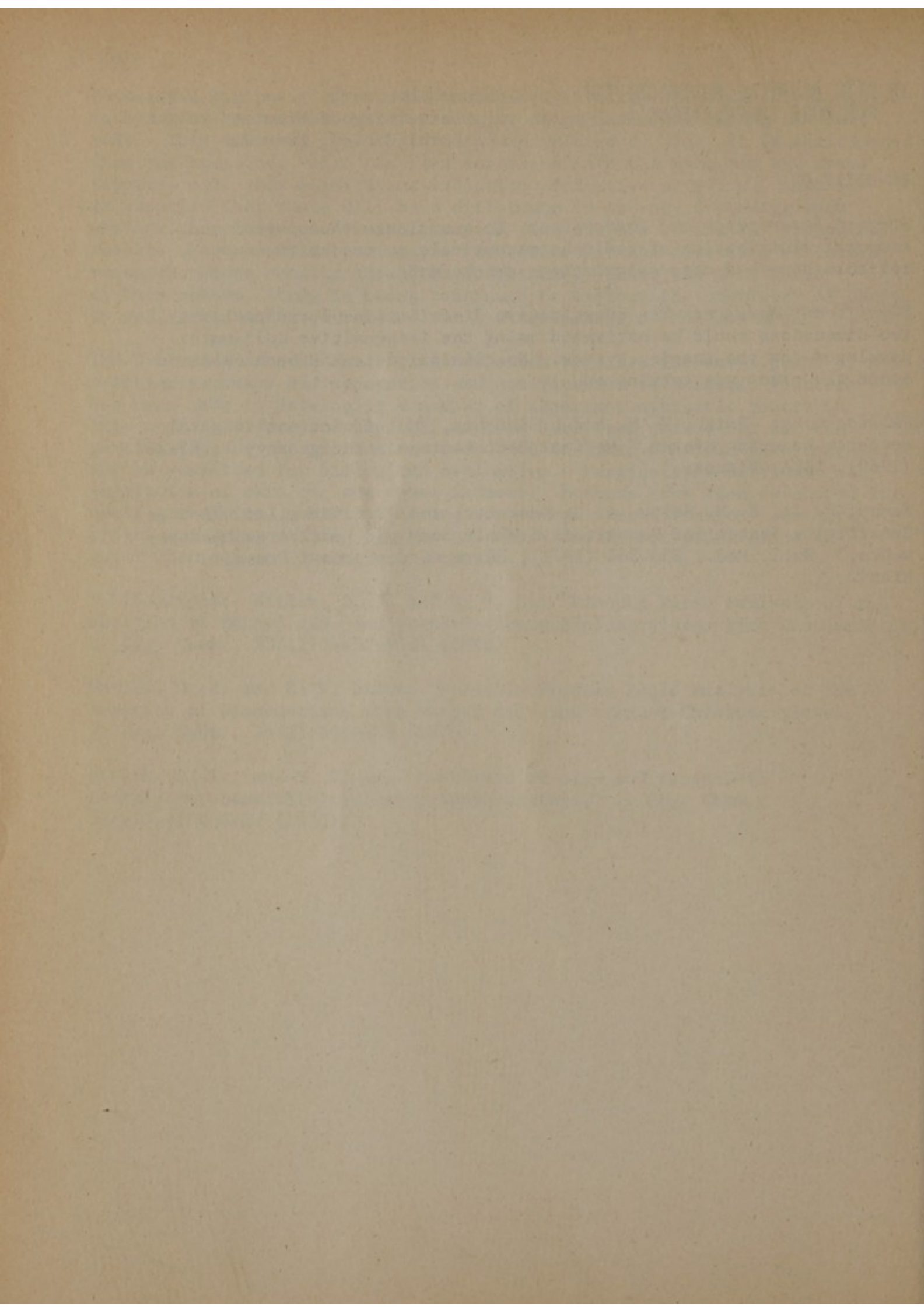
EC-00117-02

Project Description and Objectives: To quantitate the spatial and temporal distribution of radiopharmaceuticals in man so that more reliable absorbed dose calculations can be made.

Significant Results: The quantitative distribution of radioactivity in two dimensions could be estimated using the isosensitive collimator developed for the imaging system. No clinical data has been obtained since the grant was terminated.

Publications: Smith, E. M. and L. Katchis, "Multifunctional digital research scanning system," Medical Radioisotope Scintigraphy, 1:187-202 (1969), IAEA, Vienna.

Kenny, P. J., E. M. Smith, A. G. Kasenter, and J. F. Mibelli; "A High Sensitivity System for Quantitative Whole Body and Local Area Measurements," Nucl. Med., 855-864 (1971), University of Miami Press, Miami.



TV IMAGE STORAGE, ELECTRONIC
MEMORIES AND RADIOLOGY

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Medicine
Atlanta, Georgia

EC-00127-02

Project Description and Objectives: This research includes several investigations pertinent to recent developments in the fields of television image storage, electronic memory systems, and diagnostic roentgenography. These include determination of systems characteristics, adaptation of computer techniques to the production, storage and retrieval of images, and the performance of a series of controlled clinical trials to test operational hypotheses.

The major aim is to obtain the necessary fundamental data on this new x-ray television method of visualization, which will lead to new concepts of diagnostic radiology, with emphasis on significant dose reduction to the patient and environment.

Significant Results: The major purpose of this research continues to be proof of the applicability of "electronic radiography" to routine x-ray procedures for the purpose of x-ray exposure reduction and instantaneous image production. Concurrently with the clinical evaluations under way, research into the physical factors related to "electronic radiographic" image formation and storage being performed in the laboratory.

In the clinical application of "electronic radiography," the system has proven to have particular value in the performance of pediatric cystourethrography. In these cases any gonadal exposure is undesirable and must be kept to a minimum. A series of cases has been completed using x-ray factors essentially the same as those used for conventional fluoroscopy for several 1/30 second x-ray exposures. More than ample information was obtained for diagnostic interpretation with 3 to 11 seconds of x-ray exposure as compared with the 1 to 5 minutes ordinarily required. For example, where a conventional voiding cystogram would require fluoroscopy plus film radiography with a total exposure of about 4 R, equivalent diagnostic information could be obtained using electronic radiography with a total exposure of about 200 mR.

Renal biopsies are usually performed using intravenous urography and conventional fluoroscopy. Using "electronic radiography," the same number of diagnostic biopsies may be obtained, but with a decided reduction in exposure time. Approximately 30 separate x-ray images may be taken using conventional fluoroscopic technique with a total exposure time of 0.5 seconds, affording a total exposure reduction of about 98 percent.

For certain catheter positioning, while still using fluoroscopic kVp and mA, the exposure time can often be shortened from 5-10 seconds to less than 0.1 seconds.

The system has been used for two cases of fetal intrauterine transfusion, producing adequate x-ray imaging with greatly reduced equivalent exposure to the fetus. Hysterosalpingography has been performed with patient exposure being reduced to that equivalent to two seconds of conventional fluoroscopy.

During these initial clinical investigations the x-ray exposure was kept to a minimum and some deterioration in image quality was naturally present, the objective being to determine the minimum x-ray photon requirement for various types of diagnostic image information. In every instance, however, sufficient image information was obtained to accomplish the diagnostic aims.

For orthopedic procedures where the fine detail of a film radiograph was not required, reductions in exposure ranged from 1/500 to 1/1000 of that necessary to expose film. In the visualization of bones and joints, the exposure reduction afforded through the use of this system permitted the University Regional Rehabilitation Research and Training Center to proceed with a research project for investigation of hip joint parameters in susceptible populations (cerebral palsied children), the objective being the study and prevention of hip dislocations which are highly disabling to physical function. Without the low x-ray exposure "electronic radiography" system, a study of this type would be questionable due to the gonadal exposure possibilities using conventional radiographic technique.

Investigation of the physical aspects of television image production and integration as applied for "electronic radiography" confirmed that: (1) the TV camera tube has greater sensitivity and less reciprocity failure than film, and (2) the quantum integration capability of the camera tube permits use of exposure times from 1/1000 to 1/10 seconds to obtain the desired integration sensitivity.

In addition, this research lead to the development and evaluation of a large external screen x-ray image intensifier for use with the "electronic radiography" system to increase the field of view. This device proved to operate satisfactorily with the same low x-ray exposure levels as those used with the conventional intensifier; and with a much greater dynamic range.

It is felt that this research has clearly shown the diagnostic x-ray exposure reduction and imaging capabilities of "electronic radiography" systems; and will prove to be one of the milestones in the development of roentgenographic visualization techniques for the armamentarium of the radiologist and physician.

Publications: Baker, V.D., A. R. Moses, W. B. Miller, and H. S. Weens,
"Large-Screen Image Intensification," *Radiology*, 89(3):688 (1971).

The first part of the paper is devoted to a discussion of the general principles of the theory of the structure of the atom. The second part is devoted to a discussion of the experimental results obtained in the study of the structure of the atom.

The third part of the paper is devoted to a discussion of the theoretical results obtained in the study of the structure of the atom. The fourth part is devoted to a discussion of the experimental results obtained in the study of the structure of the atom.

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The nineteenth part of the paper is devoted to a discussion of the theoretical results obtained in the study of the structure of the atom. The twentieth part is devoted to a discussion of the experimental results obtained in the study of the structure of the atom.

MEDICAL PHYSICS CONFERENCE

Edward W. Webster

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Boston, Massachusetts

EC-00130-01

Project Description and Objectives: This Conference was planned to bring together a national and international group of about 600 medical physicists to explore the present state of the art of medical physics, its problems and future trends. Emphasis was placed on current research in medical nuclear physics, radiation dosimetry as it affects medical therapy and diagnosis, radiation protection in medical institutions, radiobiology as it concerns radiotherapy and radiation protection, and several other topics relating to the applications of physics and engineering in medicine including artificial limbs and organs, patient monitoring, biological measurements in hostile environments, and the medical uses of ultrasound, thermography and coherent light. In addition a primary purpose was to review the important frontiers of medical physics for the benefit of U.S. specialists in this field by means of a series of symposia given by internationally recognized specialists.

Significant Results: 243 papers including 25 invited papers presented in seven symposia were given.

Publications: Abstracts of papers - Second International Conference on Medical Physics, Inc., Boston, Massachusetts. Published in Physics in Medicine and Biology, 15:134-221 (1970).

Laughlin, J. S. and E. W. Webster, "Advances in Medical Physics," Published by Second International Conference on Medical Physics, Inc., Boston, Massachusetts, pp. 1-360 (1971).

strippable coating on porous surfaces ... and the ...
experiments with microcurie quantities of ^{222}Rn ...
daughters, yielded about the same DP's based on gamma-ray ...
for ^{222}Rn .

Publications: None.

Harvard Medical School
Boston, Massachusetts

MEDICAL PHYSICS CONFERENCE

EC-60130-01

Project Description and Objectives: This Conference was planned to bring together a national and international group of about 500 medical physicists to explore the present state of the art of medical physics, its problems and future trends. Emphasis was placed on current research in medical nuclear physics, radiation dosimetry as it affects medical therapy and diagnosis, radiation protection in medical institutions, radiobiology as it concerns radiotherapy and radiation protection, and several other topics relating to the application of physics and engineering in medicine including artificial limbs and organs, patient monitoring, biological measurements in medical instrumentation, and the medical use of ultrasound, fluoroscopy and coherent light. In addition a primary purpose was to review the present frontiers of medical physics for the benefit of U.S. specialists in this field by means of a series of symposia given by internationally recognized specialists.

Program: 243 papers including 22 invited papers presented in seven symposia were given.

Publications: Abstracts of papers - Second International Conference on Medical Physics, Inc., Boston, Massachusetts. Published in Physics in Medicine and Biology, 15:1-22 (1970).

Laughlin, J. S. and R. W. Webster, "Advances in Medical Physics," Published by Second International Conference on Medical Physics, Inc., Boston, Massachusetts, pp. 1-200 (1971).

NEW DECONTAMINATION TECHNIQUES FOR RADIUM-226

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EC-00134-01

Project Description and Objectives: The objective of the proposed research is to develop new techniques for decontaminating surfaces that have become contaminated as the result of an accident or leak involving a radioactive source containing radium-226 salts or as the result of a direct spill of radium-226 salts.

Significant Results: New techniques, including strippable coatings and liquid and solid foaming systems, were investigated for decontaminating radium from surfaces. In the initial studies, barium salts tagged with ^{133}Ba were used as simulants for radium salts. Small representative samples of various surfaces, including stainless steel, aluminum, lead, formica, ceramic tile, vinyl tile, vinyl asbestos tile, concrete, plaster, brick, blacktop, wallboard, plywood, and hardwood flooring, were prepared and contaminated with barium salts after which the new decontamination techniques were tried. The most promising technique involved the use of strippable coatings containing the chelating agent EDTA (ethylenediaminetetraacetic acid) as a reactive filler. For nonporous surfaces, the most effective coating developed was a natural rubber latex emulsion. For porous surfaces, such as unpainted concrete and brick, which are extremely hydrophilic, water must be avoided for successful decontamination. Therefore, a strippable coating having polyvinyl chloride as the binder and utilizing toluene as the solvent was developed. The decontamination factor (DF), defined as the ratio of the gamma count existing on the surface before decontamination to the gamma count rate following decontamination was about 100 for nonporous surfaces and about 4 for porous surfaces. Successive applications of the organic solvent strippable coating on porous surfaces increased the DF to about 50. Experiments with microcurie quantities of ^{226}Ra , in equilibrium with its daughters, yielded about the same DF's based on gamma count rates as for ^{133}Ba .

Publications: None.

James E. Green
Battelle Memorial Institute
Columbus, Ohio

NEW DECONTAMINATION TECHNIQUES
FOR RADIUM-226

EC-00154-01

Project description and objectives: The objective of the proposed research is to develop new techniques for decontaminating surfaces that have become contaminated in the event of an accident or leak involving a radioactive source containing radium-226 or its decay products of a direct spill of radium-226 salt.

Significant results: New techniques, including stripable coatings and liquid and solid foaming systems, were investigated for decontaminating radium from surfaces. In the initial studies, radium salts tagged with ^{137}Ba were used as standards for radium salts. Small representative samples of various surfaces, including stainless steel, aluminum, lead, limestone, ceramic tile, vinyl tile, vinyl asbestos tile, concrete, plaster, brick, blacktop, wallboard, plywood, and hardwood flooring, were prepared and contaminated with radium salts either by the new decontamination techniques were tried. The most promising technique involved the use of stripable coatings containing the chelating agent EDTA (ethylene-diaminetetraacetic acid) as a reactive filler. For nonporous surfaces, the most effective coating developed was a gummi rubber latex emulsion. For porous surfaces, such as untreated concrete and brick, which are extremely hydrophilic, water must be avoided for successful decontamination. Therefore, a stripable coating having polyvinyl alcohol as the binder and utilizing cellulose as the solvent was developed. The decontamination factor (DF), defined as the ratio of the gamma count existing on the surface before decontamination to the gamma count remaining after decontamination was about 100 for nonporous surfaces and about 4 for porous surfaces. Successive applications of the organic solvent stripable coating on porous surfaces increased the DF to about 50. Experiments with microcurie quantities of ^{226}Ra , in agreement with the daughter, yielded about the same DF's based on gamma count rates as for ^{137}Ba .

References: None.

QUANTITATIVE ORGAN VISUALIZATION
IN NUCLEAR MEDICINE

Albert J. Gilson
University of Miami
Coral Gables, Florida

EC-00135-01

Project Description and Objectives: The objective of holding this Conference is to assemble a group of the world's experts on quantitative organ visualization in nuclear medicine so that the following questions and statements can be considered:

1. What instrumentation currently exists for quantitative organ visualization and what are the capabilities and limitations of these systems?
2. Will continuation of the development of this instrumentation lead to optimal systems for quantitative organ visualization, or must new instrumentation systems be developed?
3. Specify the characteristics of an optimal quantitative organ visualization system. Can a single system for all studies be developed?
4. Evaluate the problems associated with calibrating organ visualization systems.
5. Determine whether or not quantitative organ visualization systems are or will be of value in clinical nuclear medicine, or whether their usefulness is limited to research endeavors.

Along with individual experts discussing specified topics, panels of these experts will discuss and debate the merits of various methods of approaching and solving the problems associated with quantitative organ visualization.

After the Conference is completed the results will be published and widely disseminated so that the conclusions and information gained will be readily available to the science community.

Significant Results: Not applicable.

Publications: Kenny, P. J. and E. M. Smith, editors, "Quantitative Organ Visualization in Nuclear Medicine," University of Miami Press (1971).

Robert A. Welch
University of Miami
Coral Gables, Florida

QUANTITATIVE ORGAN VISION
IN HUMAN MEDICINE

62-00113-01

Abstract: This paper is a review of the literature on the quantitative measurement of human vision. The objective of this paper is to provide a summary of the current state of knowledge in this field. The paper is organized into three main sections: (1) a review of the literature on the quantitative measurement of human vision; (2) a discussion of the methods used in the quantitative measurement of human vision; and (3) a discussion of the applications of the quantitative measurement of human vision.

1. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

2. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

3. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

4. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

5. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

6. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

7. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

8. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

9. The quantitative measurement of human vision is a complex task. It involves the measurement of a wide range of visual functions, including visual acuity, visual field, visual evoked potentials, and visual evoked potentials. The measurement of these functions is typically done using a variety of methods, including psychophysical methods, physiological methods, and imaging methods.

IONIZING RADIATION BEHAVIORAL
DEVELOPMENT AND AGING

Ernest Furchtgott

University of South Carolina
Columbia, South Carolina

EC-00143-01

Project Description and Objectives: To determine the behavioral effects of ionizing radiation administered during the developmental period. The effects of age at the time of exposure as well as dose will be determined. Different types of functions, simple as well as complex, will be investigated. Animals will be studied throughout their lifespan to see whether the effects of irradiation remain constant, or whether they become exacerbated or ameliorated. The latter aspect of the research also should provide data for an analysis of behavioral changes during aging. The interrelationship of the various changes may provide us with a model for a behavioral embryology.

Significant Results: There have been some research reports according to which rats irradiation *in utero* on day 18 of gestation with 1 R of x-rays showed deficits in conditioning as adults. Since this is by far the smallest quantity of irradiation reported to induce relatively permanent changes, an attempt was made to replicate this work. In a series of experiments with the Kotlyarevsky technique it has not been possible to observe deficits even with doses of 50 R, although animals exposed to 100 R did show changes on some, but not all indexes of conditioning.

In other experiments prenatally irradiated rats (50 to 200 R) were tested in various kinds of aversive conditioning situations. Here, too, no permanent changes could be observed in animals exposed to 50 R, but animals which has received 200 R showed large changes. In addition, there was a relationship between task difficulty and the response observed using drugs affecting the central nervous system. Thus, it is inappropriate to say that prenatal x-irradiation induces deficits in conditioning.

Some preliminary observations have indicated changes in the maternal behavior of irradiated rats and in the behavior of nonirradiated rats toward irradiated pups. Thus some of the previous findings of deviant behavior in adult rats exposed to ionizing radiation during development is associated with some of the changes observed in the mother-pup interaction prior to weaning. However, these changes cannot account for all of the observed deficits in adult rats which had been exposed in utero.

Note: This project was previously supported at the University of Tennessee, Knoxville, Tennessee under grant number EC-00070-14.

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Furchtgott, E., R. K. Lore, and W. G. Morgan, "Depth Perception in Prenatally X-Irradiated Rats," *Percept. Mot. Skills*, 15:703-710 (1964).

Furchtgott, E. and E. E. Cureton, "Factor Analysis of Emotionality and Conditioning in Mice," *Psychol. Rep.*, 15:787-794 (1964).

Dees, J. W. and E. Furchtgott, "Drive Generalization," *Psychol. Rep.*, 15:807-810 (1964).

Furchtgott, E., "Radiation as a Tool in Studies of Behavioral Age Changes," *Behavior, Aging and the Nervous Systems*, Charles C. Thomas, publisher, pp. 1-11 (1965).

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Walker, S. and E. Furchtgott, "Effects of Prenatal X-Irradiation on the Acquisition, Extinction and Discrimination of a Classically Conditioned Response," *Rad. Res.*, 42(1):120-128 (1970).

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Furchtgott, E., "Behavioral Effects of Ionizing Radiations," *Pharmacological and Biophysical Agents and Behavior*, pp. 1-64 (1971).

STUDIES IN RADIATION PROTECTION

Robert R. Kuntz
University of Missouri
Columbia, Missouri

EC-00190-06

Project Description and Objectives: To clarify the molecular mechanisms of radiation damage to a system and chemical protection from this damage. These studies, conducted on model systems are designed to provide information which may be used for a quantitative prediction of the rate and mechanism by which damage will occur as a function of the molecular structure of the species exposed to the radiation. Such studies are expected to lead to development of more effective chemical protectors.

Significant Results: Studies of the molecular mechanism for decomposition of radiosensitive compounds of biological importance have been the subject of investigations during the past year.

The indirect attack route for the decomposition of amino acids by free radicals produced in the deposition of energy in radiolysis systems has been investigated using the methyl radical as a model attacking species. Results show that free radicals attack only the α -carbon on aliphatic amino acids and the side chain exerts only steric effects on the reaction rate.

The direct decomposition of cysteine by ultraviolet light simulates the environment of cysteine or a cysteine-like molecule which is excited directly by ionizing radiation. The yield of atomic hydrogen from this process has been determined and the rate of H-atom attack on the -SH group has been measured using a competition technique. This rate constant is nearly as large as that observed for the OH radical.

The mechanism by which H-atoms react with radiation protectors and radiation sensitizers has been measured in a radiolytic system as a function of pH. A significant mechanistic difference appears, in this mechanism, between thiols which act as protectors, and those that act as sensitizers. These results are presently being confirmed for possible exploitation as a probe to determine the protective potential of a compound.

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CELLULAR LOCALIZATION OF XENON BY
MICRORADIOGRAPHY

Robert J. Schulz

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EC-00199-04

Project Description and Objectives: It has been shown in this laboratory that xenon gas, in the presence of oxygen, markedly potentiates the effects of x-irradiation. Because xenon is chemically inert, the site and mechanism of its potentiating action are of great importance in radiobiology. Using the methods of microradiography an attempt will be made to localize xenon at the intracellular level and to quantitate the amount of xenon present at specific sites.

Significant Results: It has been discovered that mammalian cells are sensitized to x-radiation when they are exposed to xenon gas at the time of irradiation. Specifically, HeLa cells exposed to xenon at a partial pressure of 3.5 atmospheres have a mean lethal dose one half that of cells exposed to air. This is opposite to earlier investigations by Hornsey et al and Evans et al that showed xenon to provide an anoxic type of protection to the bean root and the mouse respectively. No experiments connected with this project to date have resulted in an explanation for these differences in response. However, it has been demonstrated that similar sensitization is obtained in the Chinese hamster cell and it is likely that all mammalian cells will respond approximately the same way.

Studies have also been extended to the inert gases krypton and argon. These gases also sensitize HeLa cells to the effects of x-irradiation but much higher pressures are required. It has been observed that there is a direct correlation between the gas pressure required to achieve a given level of sensitization and the quantity of the gas dissolved in cellular lipids. It is expected that concurrent microradiographic studies of xenon cellular distributions will help to elucidate the mechanisms of inert gas sensitization.

Microradiographic studies of normal HeLa cells are well underway. Although current techniques clearly show nuclear detail such as individual nucleoli, the cytoplasm remains largely unresolved because in the plated cell it is only a fraction of one micron thick. Modifications in the microradiographic apparatus will permit softer x-ray beams to be used and these should permit visualization of cytoplasmic structure.

Apparatus for localizing xenon within the HeLa cell has been completed and is currently being tested. This will require freezing the cells containing xenon to below the freezing point of xenon, -112°C , and then

making the microradiography. Many technical problems have had to be overcome; however, the first microradiographs of deep-frozen, hydrated cells are now in hand. These will be used as a reference for the first xenon localization studies.

Publications: Schulz, R. J., A. M. Markoe and R. Anigstein, "Xenon: Effect on Radiation Sensitivity of HeLa Cells," *Science*, 163:571-572 (1969).

During FY 1971 the following research grants were transferred to the Environmental Protection Agency:

Health and Safety Studies	Environmental Laboratory and Health Studies
Environmental Effects of the	Robert C. Anderson
Construction of the	University of Utah
10-0000-01	Salt Lake City, Utah
Effects of Fly Ash on Fishes	Robert C. Anderson
and the Environment	University of Utah
10-0000-02	Salt Lake City, Utah
Biological Effects of	Francis J. Anderson
Heavy Metals	University of Utah
10-0000-03	Salt Lake City, Utah

RESEARCH GRANTS TRANSFERRED TO EPA - FY 1971

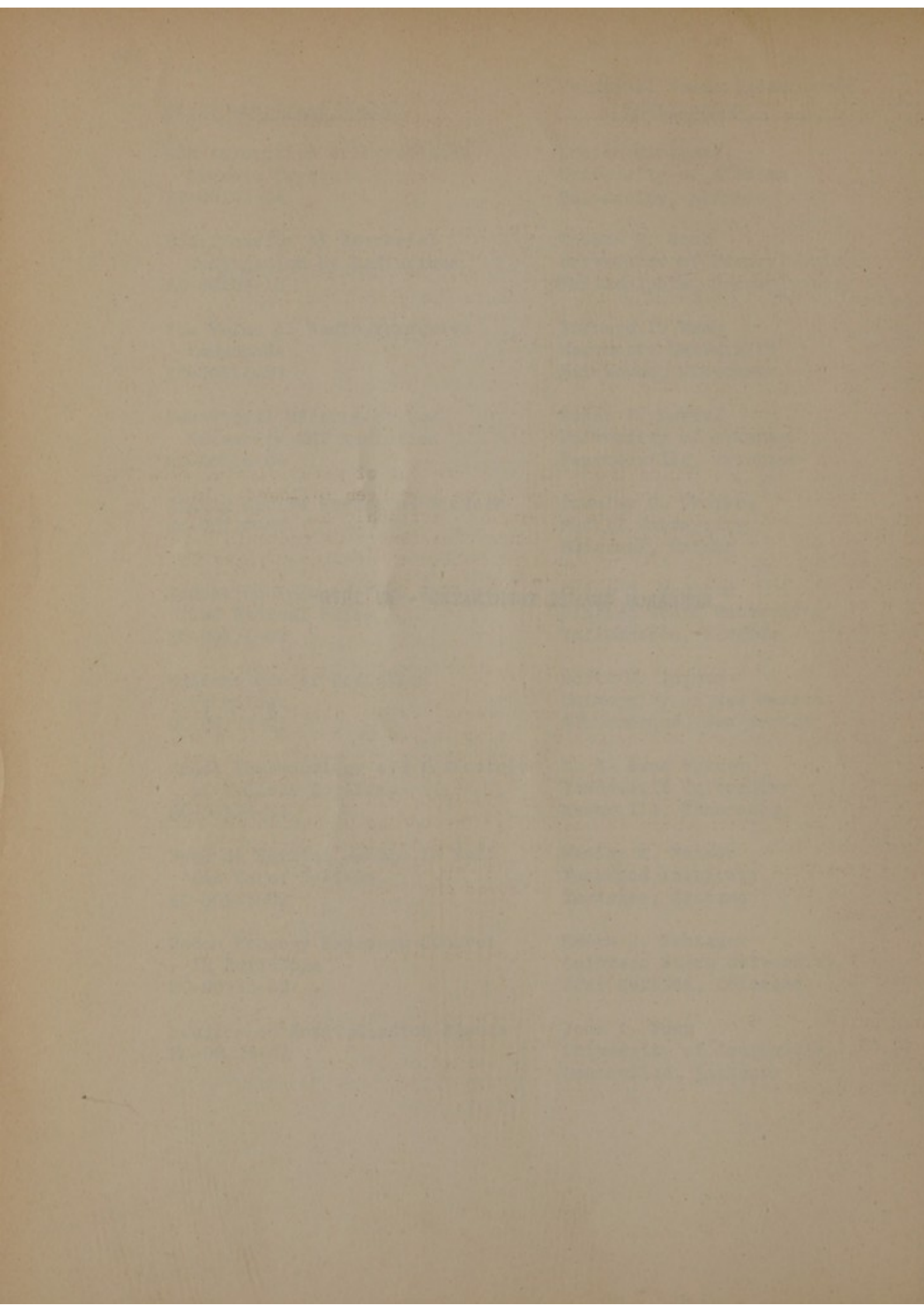
Environmental Effects of	Joseph C. Anderson
Heavy Metals	University of Utah
10-0000-04	Salt Lake City, Utah
Biological Effects of	Michael Wilson
Heavy Metals	University of Utah
10-0000-05	Salt Lake City, Utah
Biological Effects of	Robert C. Anderson
Heavy Metals	University of Utah
10-0000-06	Salt Lake City, Utah
Biological Effects of	Robert C. Anderson
Heavy Metals	University of Utah
10-0000-07	Salt Lake City, Utah
Biological Effects of	Robert C. Anderson
Heavy Metals	University of Utah
10-0000-08	Salt Lake City, Utah
Biological Effects of	Robert C. Anderson
Heavy Metals	University of Utah
10-0000-09	Salt Lake City, Utah
Biological Effects of	Robert C. Anderson
Heavy Metals	University of Utah
10-0000-10	Salt Lake City, Utah

During FY 1971 the following research grants were transferred to the Environmental Protection Agency.

<u>Title and Grant Number</u>	<u>Principal Investigator and Institution</u>
Environmental Effects on the Content of Cs-137 in Milk EC-00067-09	Robert C. Pendleton University of Utah Salt Lake City, Utah
Follow-up Study of Patients Who Received Thorotrast and of Control Group EC-00068-10	Jorge da Silva Horta University of Lisbon Lisbon, Portugal
Radiolysis of Heterogeneous Systems EC-00077-07	Francis J. Johnston University of Georgia Athens, Georgia
β -Irradiation Effects on Dermal Vascular Permeability EC-00079-08	Joseph Tabachnick Albert Einstein Medical Center Philadelphia, Pennsylvania
Radiation Protection and Recovery in Germfree Animals EC-00080-08	Raphael Wilson University of Notre Dame Notre Dame, Indiana
Displacement Reaction of Anti-Radiation Drugs EC-00083-08	Robert E. Davis Purdue Research Foundation Lafayette, Indiana
Comparative Effects of Two Radiation Exposure Regimes EC-00101-06	Donald G. Willhoit University of North Carolina Chapel Hill, North Carolina
Tooth Collection for Radioactive Nuclide Study EC-00102-09	Harold L. Rosenthal Washington University St. Louis, Missouri
Late Effects of Thorium Dioxide Retention in Humans EC-00108-04	Murray L. Janower Massachusetts General Hospital Boston, Massachusetts

<u>Title and Grant Number</u>	<u>Principal Investigator and Institution</u>
ESR Absorption of Irradiated Organic Crystals EC-00103-04	Ichiro Miyagawa University of Alabama University, Alabama
Modification of Bacterial Conjugation by Radiations EC-00109-16	Thomas H. Wood University of Pennsylvania Philadelphia, Pennsylvania
The Value of Radioprotective Compounds EC-00111-03	Richard I. Wang Marquette University Milwaukee, Wisconsin
Behavioral Effects of Low Intensity UHF Radiation EC-00116-04	Susan F. Korbel University of Arkansas Fayetteville, Arkansas
Highly Active Strontium Binders EC-00120-03	Stanley C. Skoryna McGill University Montreal, Canada
Radiation Induced Free Radicals and Radical Pairs EC-00121-02	Grace C. Moulton Florida State University Tallahassee, Florida
Macromolecular Radiation Pathology EC-00123-03	Scott W. Jordan University of New Mexico Albuquerque, New Mexico
Renal Pharmacology and Toxicology of Fallout Nuclides EC-00128-03	B. V. Rama Sastry Vanderbilt University Nashville, Tennessee
Fate of Harmful Metals in Soil and Water Systems EC-00145-02	Wesley E. Nelson Tuskegee Institute Tuskegee, Alabama
Radon Progeny Exposure Control In Buildings EC-00153-02	Keith J. Schiager Colorado State University Fort Collins, Colorado
Studies on Antiradiation Agents EC-00204-02	John L. Wong University of Louisville Louisville, Kentucky

RESEARCH GRANTS TERMINATED - FY 1970



BIOLOGICAL ENRICHMENT CHAINS OF
RADIONUCLIDES IN FINNISH LAKES

Jorma K. Miettinen
University of Helsinki
Helsinki, Finland

EC-00087-05

Project Description and Objectives: The purpose of the project is to elucidate the limnological factors affecting the accumulation of the biologically most important radionuclides in fresh water organisms, especially fish. Food chains of ^{137}Cs from the global fallout will be studied in 12 lakes of limnologically different types (from nutrient deficient ones to those rich in nutrients). In addition, isotope labelling experiments will be carried out with ^{137}Cs , ^{85}Sr , ^{131}I , ^{140}Ba and ^{45}Ca in five lakes of different limnological types in order to determine quantitatively the changes with time in the distribution of the isotope between different compartments of the lake biosystem.

Significant Results: Since 1963 the ^{137}Cs content of water plants, plankton and various fish species in 10 Finnish lakes have been followed. In most species maximum values were observed in eutrophic lakes in 1964 and in oligotrophic lakes in 1965. Since then the ^{137}Cs contents have decreased exponentially with an apparent half-time of 2 to 4 years in plankton and fish and 3 to 4 years in the plant species studied. The rate of decrease also depends on the trophic type of the lake, being usually faster in eutrophic lakes.

A total balance experiment was carried out in a small dysoligotrophic lake by pumping $4\text{mCi } ^{131}\text{Ba}$ from a moving boat and mixing it homogeneously into the productive layer. For several weeks, water, plankton, plants and fish were analyzed periodically. Accumulation of the nuclides continued in most species for 5 to 7 days, when their equilibrium was reached. Enrichment factors reached ($\text{pCi/kg fr wt/pCi/litre water}$) were in plankton $4 - 26 \cdot 10^5$, in plants 700-1800, and in fish 2000-4000 except in small perch where it was 2300. The uptake of barium was much slower than that of calcium, which was studied earlier. During the whole experiment only 40 percent of ^{131}Ba was removed from the water, while this removal of calcium took place on the first day of the experiment.

Publications: Miettinen, J. K., "Radioaktiva Naringskedjor I Lappland," Sartryck ur Naringsforskning Nr 4 (1965).

Hasanen, E., S. Kolehmainen, and J. K. Miettinen, "Biological Half-Time of ^{137}Cs in Three Species of Fresh Water Fish: Perch, Roach and Rainbow Trout," International Symposium on Radioecological Concentration Processes in Stockholm, April 25-29, 1966.

Kolehmainen, S., E. Hasanen, and J. K. Miettinen, "¹³⁷Cs Levels in Fish of Different Limnological Types of Lakes in Finland During 1963," Health Phys., 12:917-922 (1966).

Kolehmainen, S., S. Takatalo, and J. K. Miettinen, "A Tracer Experiment with I-131 in an Oligotrophic Lake," Proceedings of the 2nd National Symposium, Ann Arbor, Michigan (May 15-17, 1967).

EC-00088-06

Project Description and Objectives: To investigate protection against the lethal effects of whole body irradiation by bone marrow transplantation. Two major and necessary correlative studies include:

1. Methods of maintaining life during periods of bone marrow failure. These techniques will include maintenance of electrolyte and water balance, prevention and control of infection, provision of platelets and provision of large numbers of granulocytes.
2. Studies of the immunological complications of marrow transplantation. These will include studies of the nature of the immunologic reactions responsible for graft rejection or graft-versus-host disease and studies of means of control of immunologic reactions using immunosuppressive drugs, antilymphocyte serum and extracorporeal irradiation.

Significant Results: The individual exposed to a high dose of whole body irradiation is in danger of death from bleeding and infection because of destruction of the very sensitive bone marrow that produces platelets and white blood cells. A transplant of normal bone marrow would obviously be desirable, but the physician caring for such a patient is confronted with a dilemma in that (a) if the irradiation exposure is sublethal a transplant is not needed and might be dangerous since there is evidence in mice that an attempted marrow transplant might be harmful, or that (b) if the transplant is successful there is danger of graft-versus-host disease. Clearly the risk of graft-versus-host disease should be accepted if lethality is certain otherwise, but the irradiation exposure is not usually known with certainty in irradiation accidents. Accordingly, it seemed worthwhile to explore, in dogs, radiation exposures (400-600 R) that are in the range of mid-lethal to lethal doses. The studies were carried out under well-standardized conditions where marrow grafts are consistently achieved after very high radiation exposures (1200 R). Unrelated donors and recipients were used.

A comparison of survival times, white blood cells and platelet counts and marrow histology at all 3 radiation exposures showed no difference in the animals given marrow and the controls. Marrow grafts did not occur and no harmful effect of the marrow transplant could be demonstrated. On the other hand, dogs whose own marrow had been frozen prior to the experiment and readministered after the irradiation exposure all survived. It is likely, therefore, that the irradiation

accident victim will not benefit from an attempted marrow transplant unless marrow from an identical twin or close relative or marrow selected by histocompatibility typing is available.

In another study involving unrelated dogs, the marrow from the donor was preserved by freezing to -80°C in 10 percent dimethyl sulfoxide. (Earlier studies had shown that marrow can be kept for years at low temperatures.) At the time of freezing the marrow was "typed" using 8 canine histocompatibility typing sera. After administration of 1200 R to the recipient, the donor marrow was thawed and administered intravenously. The results in 10 recipients that were matched with their donors were compared with the results in 10 mismatched recipients. The results showed clearly that matched recipients survived significantly longer than did the mismatched ones. Two of the matched dogs became permanent chimeras and are alive and well more than one year later. These experiments indicate the feasibility of setting up a "marrow bank" using human marrow that has been typed histocompatibility typing sera that have been developed in connection with the human kidney transplant program. From such a pool of preserved marrow specimens, an appropriate donor marrow could be selected on the basis of the recipients histocompatibility type.

Publications: Epstein, R. B., J. W. Eschbach, Jr., and E. D. Thomas, "Prolongation of Skin Graft Survival by Methotrexate and Cross Circulation," *Transplantation*, 3(4):484-489 (1965).

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Eschbach, J. W., Jr., R. B. Epstein, J. M. Burnell, and E. D. Thomas, "Physiologic Observations in Human Cross Circulation," *N. Engl. J. Med.*, 273:997-1003 (1965).

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LOW LEVEL GAMMA RADIATION AND
PHYSIOLOGICAL PERFORMANCE

George M. Krise
Texas A & M Research Foundation
College Station, Texas

EC-00089-05

Project Description and Objectives: To test the effects of virtually continuous (20 hours per day) exposure to various relatively low doses of ionizing radiation on the ability of the test animal, the Spanish goat, to perform both reproductively and physiologically.

Significant Results: During this terminal year the 7 R and 2 R per day animals reached their median to death time. As in other exposure groups of this series the females succumbed to these low levels of radiation before the males. The median survival time for 7 R exposed animals was 366 days for females and 1152 days for males. A group of goats were exposed at an intermediate exposure level of 15 R per day to bridge the gap between the 7 R and 30 R per day exposures. The median survival time for these 15 R per day exposed animals was 161 days for females and 240 days for males. In addition to these data the hematological studies, physiological performance studies and semen analysis studies were included in the data presently being processed.

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LONDON

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BRITISH ANTHROPOLOGICAL SOCIETY

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DIGITAL COMPUTING TECHNIQUES IN
RADIOLOGICAL PROBLEMS

John L. Howarth
University of New Mexico
Albuquerque, New Mexico

EC-00093-04

Project Description and Objectives: The application of computer techniques to radiological problems with particular reference to the following:

1. The computation of doses near boundaries in inhomogeneous media irradiated with ionizing radiations, with particular reference to soft-tissue cavities in bone.
2. The development of mathematical models for the growth and dissemination rates of malignant tumors.
3. Calculations of the gamma-ray energy absorbed in bodies of different shapes containing distributed radioactive materials and of other miscellaneous data of interest in radiology.

Significant Results: Further calculations have been made of doses near boundaries in inhomogeneous absorbers irradiated with x-rays with particular reference to soft tissue cavities in bone. The theory has been extended to cover continuous x-ray spectra. Some further progress has been made in deriving mathematical models for growth and dissemination rates of malignant tumors, with the intention of improving estimates of prognosis in such cases.

Publications: None.

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CHELATION IN RADIATION PROTECTION
CHEMICALS

Seymour S. Block
University of Florida
Gainesville, Florida

EC-00095-03

Project Description and Objectives: To better understand the mechanism of chemical protectants against ionizing radiation and to be able to produce more effective and useful materials. More specifically, it is planned to synthesize and study the effect of protectant compounds that are capable of chelation. The effect of chelation on radiation protection is being investigated by producing a series of compounds that have the same reactive structure and are known to chelate and to be radioprotective, but to introduce substituents in the nonreactive part of the molecule, which will influence the electrical properties and thereby the ability to chelate. Synthetic work for preparation of new compounds is described.

Significant Results: Our research has demonstrated that the radiation effect on ribonuclease is very complex, comprising both chemical and physical damages to the molecule; some of these are irrelevant to enzyme activity, while others destroy the activity of the enzyme. Present evidence indicates that the radiation effect is mediated through reactive free radicals formed from water. Since every biological system must be regarded as essentially an aqueous medium, it is clear that research should be addressed to the study of these free radicals and their effects. Through such work, we can hope to acquire additional knowledge of means to enhance or minimize radiation effects.

Publications: Block, S. S., D. D. Mulligan, J. P. Weidner, and D. G. Doherty, "Chelation and Radiation Protection," Rad. Protection and Sensitization, Rome (May 1969).

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HEMATOLOGIC RESPONSES TO NON-HOMOGENEOUS IRRADIATION

Donald G. Willhoit
University of North Carolina
Chapel Hill, North Carolina

EC-00105-03

Project Description and Objectives: (1) To determine if changes in the peripheral blood following partial body exposure may be used as indicators of lethal radiation injury. (2) To develop expressions for dose and dose distribution factors for non-uniform radiation exposure.

Significant Results: Hematologic studies were conducted on rats exposed to either whole-body, upper-body, or lower-body x-irradiation. For each of the three exposure conditions studied, there was an immediate drop in the lymphocyte count which was related to the magnitude of the dose. The decrease in the lymphocyte count was greatest under whole-body exposure conditions and least under upper-body irradiation conditions. This is attributed to the relative amounts of lymphocyte-producing tissues irradiated. There was a corresponding increase in the neutrophil count 3 to 6 days after exposure in each of the three groups studied and also appears to be related to dose but in a different manner than the decrease in lymphocyte count. An increase in the hematocrit values was observed in the lower-body high-dose group which reflects fluid balance disturbances due to injury to the gastro-intestinal tract. An increase in the hematocrit value was also observed in the upper-body high-dose group but occurred approximately 6 to 9 days after exposure. The results were interpreted in terms of a time-integrated mathematical expression, termed "Cumulative Response Score." This expression enables the time dependent blood responses following irradiation to be expressed as a single number, reflecting both the magnitude and duration of hematologic abnormality. These data indicate that lower-body irradiation is more effective than upper-body irradiation in eliciting hematologic response, due to the amount of bone marrow exposed. The cumulative response score does not however, appear to be a useful predictor of lethal injury for upper-body exposure and only of limited value for lower-body exposure. This is probably due to the fact that other than hematopoietic injury processes are contributing to death from upper and lower body exposures.

Publications: Willhoit, D. G., "Comparative Effects of Daily Fractionated and Continuous Irradiation on the Survival Time of Mice," ESE Notes 6(4):1-2 (1969).

THE JOURNAL OF THE
ROYAL ANTHROPOLOGICAL INSTITUTE
PART II. - PHYSICAL ANTHROPOLOGY
1901

CYTOGENETICS OF IRRADIATED
MALE MICE

Allen B. Griffen
Jackson Laboratory
Bar Harbor, Maine

EC-00107-03

Project Description and Objectives: To determine the extent of permanent radiation damage to spermatogonial stem cells in the mammalian testis after exposure to ionizing radiation. In this study, cytologically visible major chromosome aberrations, particularly translocations, are the chief indicators of damage and are readily demonstrated in the offspring of irradiated male mice.

Significant Results: It has long been assumed that after testicular irradiation male mammals (and men in particular) might refrain from procreation for a period of two or three months, and thereafter sire offspring which would be free of radiation-induced mutations and aberrations. The present study conclusively shows this assumption to be wrong, since radiation damage to testicular stem cells is permanent and permanently transmissible. It strongly points up the necessity for caution and protection in medical diagnostic and therapeutic procedures, as well as in accidental irradiation from nuclear warfare and atomic devices.

The earlier findings in this project greatly influenced two international reports on genetic risks to man (United Nations Scientific Commission on the Effects of Atomic Radiation, and International Commission on Radiation Protection), according to a reviewer of a paper submitted for publication in the Canadian Journal of Genetics and Cytology. The continuation of this study will provide a highly accurate determination of testicular damage from low doses of irradiation such as may be anticipated for human beings in the atomic age.

Publications: None.

IN VIVO REPAIR MECHANISM IN IRRADIATED ANIMALS

Jack Schubert

University of Pittsburgh
Pittsburgh, Pennsylvania

EC-00112-02

Project Description and Objectives: To investigate systematically the mechanisms by which nonlethal doses of cyanide modify the actions of ionizing radiation in mammalian systems. The approach utilizes the kinetic patterns of cyanide-induced inhibition and recovery of tissue cytochrome oxidase *in vivo* and *in vitro* as a problem with which to explore the time relations and nature of the primary biochemical processes involved in the damaging action of ionizing radiations. It has recently been found that there exists a relationship between the degree of radioprotection by cyanide and the length of time cytochrome oxidase remains in the inhibited state. It is hoped that the proposed investigations will lead to new and improved chemical means for prophylactic and therapeutic treatment of radiation injury as well as new approaches to the enhancement of tissue radiosensitivity. If a functional relationship between cytochrome oxidase activity and radiation action is established, then it is hoped, in addition, that a new approach to cancer radiotherapy can be developed in which the radiosensitivity can be increased by unprecedented factors of ten or more prior to radiotherapy. Such an approach, involving the use of penicillamine for depleting copper, hence reducing cytochrome oxidase, has already yielded impressive results in the treatment of advanced melanoma in humans. Experimental studies along these lines are planned in order to confirm the validity of this approach.

Significant Results: Many drugs can protect animals given a lethal dose of irradiation from dying. How do these drugs work? The answer to this question will not only expedite the development of new and better drugs, but will also provide new approaches to a related problem--the selective killing of cancer cells by irradiation. A detailed investigation is being made on one of the most effective radiation-protective chemicals, namely cyanide. When a single non-harmful dose of cyanide is administered to rats or mice prior to their exposure to a radiation dose which kills 100 percent of the animals, all of the cyanide-treated animals survive. Why? It has been found that the protection depends on the time elapsed between the time the cyanide was given and the end of irradiation. For example, complete survival of mice given a 100 percent deadly dose of radiation was obtained even if 12-15 minutes elapsed, while with rats a 20-25 minute interval still permitted complete survival. The increased survival of cyanide-treated animals is accompanied by a substantial reduction in the number of damaged chromosomes--the cell structures carrying the hereditary material (DNA).

the pattern of protection afforded by cyanide to irradiated animals parallels the time at which the enzyme begins to function again. Cyanide protects the animals by rendering their cells relatively resistant to the expression of radiation damage by stopping DNA synthesis and energy producing processes. At a critical stage, however, the enzyme activity resumes, making energy available to the cell so that the damage produced by radiation can be repaired.

Aside from pointing the way to more effective treatment of radiation sickness, investigations provide a rational biochemical basis for developing procedures to kill irradiated cancer cells more effectively.

Publications. None.

THERMOLUMINESCENCE OF RUBY
AND IONIC CRYSTALS

William G. Buckman
Western Kentucky University
Bowling Green, Kentucky

EC-00118-02

Project Description and Objectives: Some materials' thermoluminescent properties have made them useful as radiation dosimeters which are complementary to and competitive with the film badge for personnel radiation dosimetry. The thermoluminescent yield and spectral emission of ruby and ionic crystals will be measured. The spectral emission dependence on temperature will be determined for luminescence produced by different modes of excitation.

Significant Results: During the past year, significant results pertaining to the ultraviolet excitation of sapphire and gamma irradiated lithium fluoride, the thermoluminescence of ruby and sapphire after x-irradiation, and the fluorescence spectral emission of sapphire as a function of temperature have been obtained.

The results from this research detail the response of sapphire to ultraviolet radiation. It concludes that sapphire is sensitive (~ 10 watt/cm²), has a linear response for low radiation levels, has stable storage for at least eight days, and is virtually unaffected by normal room light. Since ultraviolet radiation has many technical applications and has many deleterious effects on man (conjunctivitis of the eye, skin cancer, and sunburn), steps are being taken to apply for a patent using sapphire as an ultraviolet detector.

Preliminary results on using gamma irradiated lithium fluoride as an ultraviolet detector have been obtained. This shows promise as an ultraviolet detector for germicidal lamps and further experiments are in progress.

The results of the thermoluminescence of ruby and sapphire have also been set out in detail. The sapphire is approximately as sensitive to x-rays as is the widely used Harshaw TLD-100 thermoluminescence powder. In addition, the stopping power response of sapphire is similar to bone, thus it can be used when one wishes to determine the absorbed x-ray energy in bone (such as in bone cancer treatment).

Interesting variations in the spectral emission of sapphire undergoing continuous x-irradiation have been observed. At 300°C, the chromium trace impurity R-lines and charge exchange region (6600-7100Å) predominate, while at 25°C the broad emission spectra near 3,000Å predominates. This indicates that similar effects might be observed for common luminescent materials used in radiology.

Publications: Buckman, W. G., C. R. Philbrick, and N. Underwood, "The Characteristics of Ruby as a Thermoluminescent Radiation Dosimeter," Proceedings of the Second International Conference on Luminescence Dosimetry, Gatlinburg, Tennessee (1968). Available from the National Technical Information Service, Springfield, Virginia 22151.

Cooke, D. W. and D. C. Sutherland, "Thermoluminescence and Emission Spectra of X-Irradiated Ruby and Sapphire," presented to the Southeastern Section of the American Physical Society, Gainesville, Florida, November 6, 1969.

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EFFECT OF X-RAY SPECTRUMS ON
RADIOGRAPHIC QUALITY

Robert J. Schulz
Albert Einstein College of
Medicine
Bronx, New York

EC-00126-02

Project Description and Objectives: Almost all radiographic x-ray equipment is operated with 2.5mm of aluminum filtration. This filtration allows a wide spectrum of x-rays to be incident upon the patient and the width of these spectra increases with kilovoltage. It appears reasonable, and preliminary experiments bear this out, that there are optimal x-ray spectra for each type of radiographic examination; optimal in the sense of minimum patient exposure and maximum radiographic quality.

The research objectives are to measure the x-ray spectra that result from the use of various high atomic number filters whose absorption characteristics markedly reduce the range of x-ray energies present in diagnostic x-ray beams. These "monochromatic" beams will then be evaluated in terms of the radiographic quality of radiographs they produce and the level of patient exposure.

Significant Results: On theoretical grounds it can be shown that for a specific radiographic examination, minimum patient exposure and maximum radiographic information are obtained with monoenergetic x-rays. In order to test the practicality of the theoretical results it is first necessary to produce x-ray spectra that contain a range of energies considerably narrower than the range obtained when the beam is filtered by aluminum. At the same time useful x-ray intensities must be maintained so that radiographs may be made in fractions of a second without overloading the x-ray tube.

The approach to this problem has been to use high atomic filters where the K-absorption edge of the filter material is matched to the voltage applied to the x-ray tube. By adjusting the high voltage to be 1.3 times the K absorption edge, x-ray spectra containing relatively narrow ranges of photon energies are obtained. Efforts to date have centered upon the construction of high atomic number filters, development of methods for measuring x-ray spectra and the collection of a library of x-ray spectra. To this end there are now seven "thin" x-ray spectra whose peak energies span the range of energies used in diagnostic radiology. These are obtained with the following filters and applied voltages:

<u>Filter</u>	<u>Voltage</u>	<u>Filter</u>	<u>Voltage</u>
Barium	55 Kvp	Gadolinium	75 Kvp
Cerium	60 Kvp	Holmium	80 Kvp
Neodymium	65 Kvp	Gold	100 Kvp
Samarium	70 Kvp		

Currently being measured is the transmission through water of these x-ray beams, and beams having 2mm of aluminum filtration, in order to obtain a basis for comparison. Following this, an x-ray technique chart must be established and then studies will be started on radiographs of anatomical phantoms to test the premise upon which this study is based.

Publications: None.

SYMPOSIUM ON RADIONUCLIDES
RADIATION DOSE AND EFFECTS

Roger J. Cloutier
Oak Ridge Associated Universities
Oak Ridge, Tennessee

EC-00131-01

Project Description and Objectives: The objectives of this conference are to bring together the current concepts on internal dosimetry and present the methods now used to estimate internal radiation dose. Invited speakers, leaders in the field, will present various facets of the problem, exchange points of view, and define major disagreements that exist in this field. It is expected to generate some fruitful pathways for resolving some of the continuing questions on dosimetry and to suggest some innovations for research workers in the field. An important objective is to provide a current reference volume on the current state of this aspect of nuclear medicine, a resource that is definitely needed for practitioners and clinical investigators.

Significant Results: The symposium "Medical Radionuclides: Radiation Dose and Effects," was held in December 1969. Thirty-two invited speakers, three from overseas, presented papers dealing with the methods of calculating the internal radiation dose to a patient administered a radiopharmaceutical and with the biological effects observed in patients who had received radiopharmaceuticals. During the discussion periods that followed each session, many additional facets of the symposium's topic emerged. Some major disagreements were brought into sharper focus while others were resolved. Innovations for research were suggested to provide solutions to some of the problems.

The proceedings including the discussions were published within six months of the meeting and have become a current reference on radiation dose and effects. The published proceedings have reached a much larger audience than the approximately 170 persons who attended the symposium since four printings have produced a total of 3500 copies.

Publications: Cloutier, R. J., C. L. Edwards, and W. S. Snyder, eds. Medical Radionuclides: Radiation Dose and Effects. US-AEC-CONF-691212, 1970. Available from National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia 22151.

NOTE: Travel funds for this symposium were provided under grant number EC-00144-01.

THE UNIVERSITY OF CHICAGO
DIVISION OF THE PHYSICAL SCIENCES
DEPARTMENT OF CHEMISTRY
CHICAGO, ILLINOIS 60637

TO THE EDITOR:
I am writing to you to inform you of the results of our recent experiments. The data obtained from the measurements of the rate of reaction between the two substances under study, at various temperatures, are shown in the table below. It is evident from the results that the rate of reaction increases with increasing temperature, and that the activation energy for this reaction is approximately 15 kcal/mole.

The following table shows the rate constants, k , for the reaction at different temperatures. The units of k are min^{-1} . The activation energy, E_a , is 15 kcal/mole.

Temperature ($^{\circ}\text{C}$)	Rate constant, k (min^{-1})
25	0.001
35	0.005
45	0.025
55	0.125

The results of these experiments are in good agreement with the theoretical predictions based on the Arrhenius equation. The data also indicate that the reaction is first order with respect to the concentration of the reactants.

Very truly yours,
J. H. K. [Signature]
Professor of Chemistry
The University of Chicago

Enclosed for the Editor of the Journal of Chemical Physics are two copies of the manuscript of the paper entitled "The Rate of Reaction Between Two Substances at Various Temperatures".

RADIATION FACILITY FOR RESEARCH
ON FOOD

William B. Esselen
University of Massachusetts
Amherst, Massachusetts

EC-00136-01

Project Description and Objectives: During the past 12 years the University of Massachusetts has conducted research on irradiation of foods and other materials. Increasing needs for irradiation facilities have made it difficult for the grantees to depend on the use of local irradiation facilities and they wish to set up their own. The AEC has agreed to supply 50,000 curie Cobalt-60 source, building space is available in the department of Agricultural Engineering laboratories and the University has allocated \$25,000 State funds toward the cost on an estimated \$50,000 apparatus to contain the Cobalt-60 source. The purpose of this project is to provide \$25,000 in matching funds to purchase the apparatus required. As planned the departments of Food Science and Technology and of Agricultural Engineering would be prime users of the facility. However, the facility would also be available for use by other departments of the University, as well as nearby Amherst, Mt. Holyoke, and Smith Colleges in order to provide joint use of this facility to maximum advantage.

Significant Results: Not applicable.

Publications. None.

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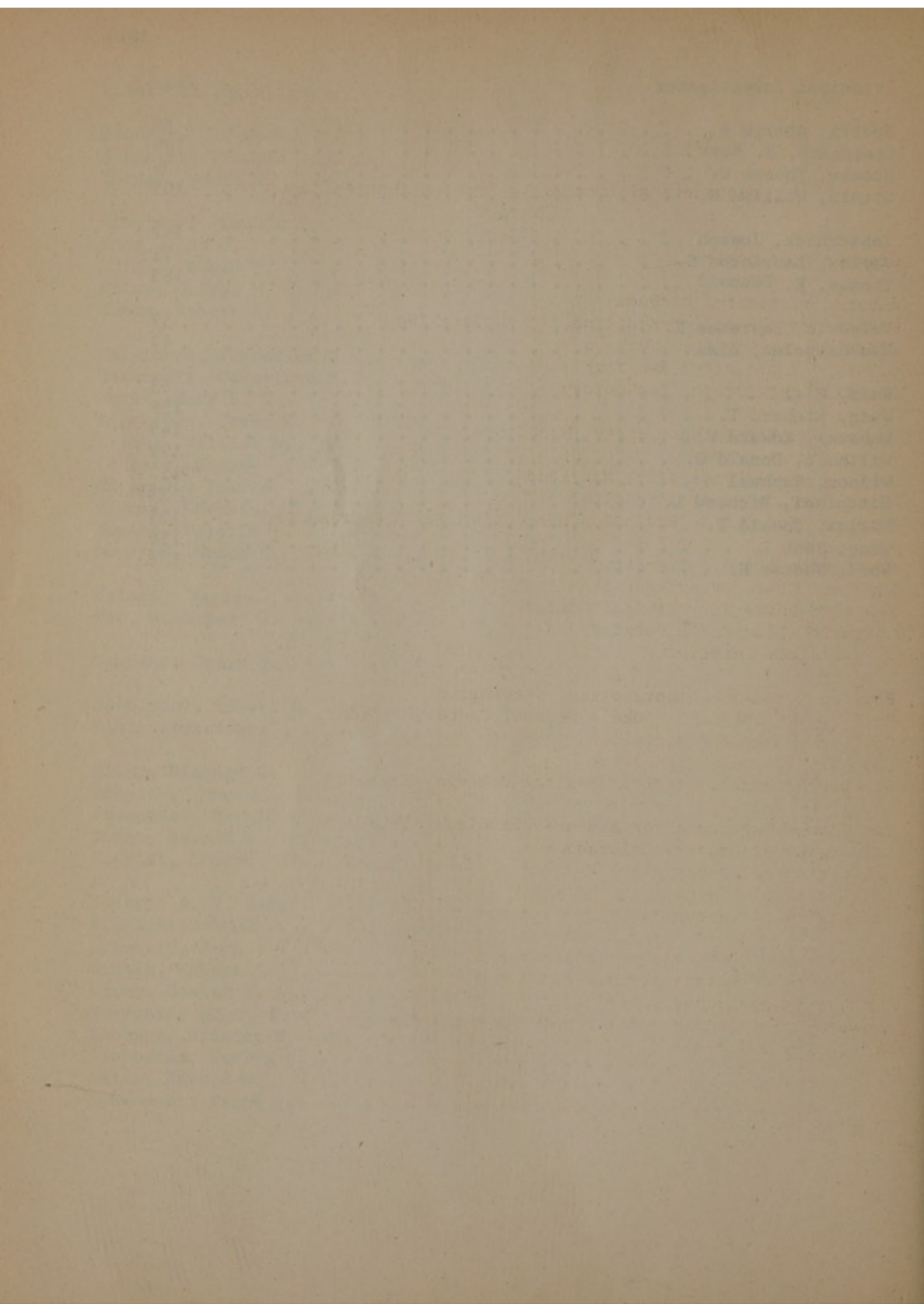
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Alphabetical Listing by Geographical Location
FY 1972

<u>State/Country</u>	<u>Grant Number</u>	<u>Page</u>
Alabama	RL 00527-01	57
California	RL 00064-10	81
Colorado	RL 00520-02	51
England	RL 00082-06	87
Georgia	RL 00412-02	43
Illinois	RL 00075-06	83
	RL 00401-01	95
	RL 00580-01	97
Indiana	RL 00104-04	93
Italy	RL 00526-03	53
Kansas	RL 00405-02	41
Kentucky	RL 00733-01	73
Maryland	RL 00433-02	45
	RL 00726-01	71
Massachusetts	RL 0065-10	9
	RL 00114-03	29
Missouri	RL 00748-01	75
New Mexico	RL 00480-02	47
New York	RL 00009-07	5
	RL 00029-06	7
	RL 00074-11	11
	RL 00078-09	15
	RL 00085-08	19

<u>State/Country</u>	<u>Grant Number</u>	<u>Page</u>
North Carolina	RL 00129-04	37
Ohio	RL 00076-09	85
Oregon	RL 00119-05	31
Pennsylvania	RL 00098-07	25
	RL 00099-18	89
	RL 00122-04	33
	RL 00575-02	63
Tennessee	RL 00511-01	49
Texas	RL 00133-03	39
Utah	RL 00534-01	61
	RL 01019-01	77
Washington	RL 00125-04	35
	RL 00528-03	59
	RL 00688-02	67
Washington, D.C.	RL 00096-07	21
	RL 00583-01	65
	RL 00695-01	69

Listing by DHEW Regions
FY 1972

<u>Region</u>	<u>State</u>	<u>Grant Number</u>	<u>Page</u>
I	Massachusetts	RL 0065-10	9
		RL 00114-03	29
II	New York	RL 00009-07	5
		RL 00029-06	7
		RL 00074-11	11
		RL 00078-09	15
		RL 00085-08	19
III	Maryland	RL 00433-02	45
		RL 00726-01	71
	Pennsylvania	RL 00098-07	25
		RL 00099-18	89
		RL 00122-04	33
		RL 00575-02	63
	Washington, D.C.	RL 00096-07	21
		RL 00583-01	65
		RL 00695-01	69
IV	Alabama	RL 00527-01	57
	Georgia	RL 00412-02	43
	Kentucky	RL 00733-01	73
	North Carolina	RL 00129-04	37
	Tennessee	RL 00511-01	49
V	Illinois	RL 00075-06	83
		RL 00401-01	95
		RL 00580-01	97
		RL 00104-04	93
	Ohio	RL 00076-09	85
VI	New Mexico	RL 00480-02	47
	Texas	RL 00133-03	39
VII	Kansas	RL 00405-02	41
	Missouri	RL 00748-01	75

<u>Region</u>	<u>State</u>	<u>Grant Number</u>	<u>Page</u>
VIII	Colorado	RL 00520-02	51
	Utah	RL 00534-01	61
		RL 01019-01	77
IX	California	RL 00064-10	81
X	Oregon	RL 00119-05	31
	Washington	RL 00125-04	35
		RL 00528-03	59
		RL 00688-02	67
Foreign	England	RL 00082-06	87
	Italy	RL 00526-03	53

Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Bureau of Radiological Health

Regional Office Information

REGION I: (Connecticut, Maine, Massachusetts, New Hampshire,
Rhode Island, Vermont)

DHEW, PHS, FDA
585 Commercial Street
Boston, Massachusetts 02109

Radiological Health Representative: Robert M. Hallisey

REGION II: (New Jersey, New York, Puerto Rico, Virgin Islands)

DHEW, PHS, FDA
850 Third Avenue
Brooklyn, New York 11232

Radiological Health Representative: Ronald E. Bernacki

REGION III: (Delaware, District of Columbia, Maryland, Pennsylvania,
Virginia, West Virginia)

DHEW, PHS, FDA
1204 U.S. Customhouse, Room 902B
Second and Chestnut Street
Philadelphia, Pennsylvania 19106

Radiological Health Representative: Robert Frankel

REGION IV: (Alabama, Florida, Georgia, Kentucky, Mississippi,
North Carolina, South Carolina, Tennessee)

DHEW, PHS, FDA
880 West Peachtree Street, N.W.
Atlanta, Georgia 30309

Radiological Health Representative: Joseph A. Brennan, Jr.

REGION V: (Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin)

DHEW, PHS, FDA
Room 1222 Post Office Building
433 West Van Buren Street
Chicago, Illinois 60607

Radiological Health Representative: James A. Kraeger

REGION VI: (Arkansas, Louisiana, New Mexico, Oklahoma, Texas)

DHEW, PHS, FDA
500 S. Ervay Street
Room 470 B
Dallas, Texas 75201

Radiological Health Representative: J. A. McTaggart, D.D.S.

REGION VII: (Iowa, Kansas, Missouri, Nebraska)

DHEW, PHS, FDA
1009 Cherry Street
Kansas City, Missouri 64106

Radiological Health Representative: William H. Oates, Jr.

REGION VIII: (Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming)

DHEW, PHS, FDA
Room 500
U.S. Customhouse
Denver, Colorado 80202

Radiological Health Representative: Bobby L. Dillard

REGION IX: (Arizona, California, Hawaii, Nevada, Guam, American Samoa)

DHEW, PHS, FDA
Federal Office Building
50 Fulton Street
San Francisco, California 94102

Radiological Health Representative: Morgan S. Seal

REGION X: (Alaska, Idaho, Oregon, Washington)

DHEW, PHS, FDA
Room 5003, Federal Office Building
909 First Avenue
Seattle, Washington 98104

Radiological Health Representative: David H. Flora

SECTION XI: LABORATORY AND OTHER SERVICES, Washington, D.C.

Room 5001, Federal Office Building
909 First Avenue
Seattle, Washington 98101

Biological Health Department: David H. Plores
Director

Section Chief: David H. Plores

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Edited by: Elisabeth H. Boeker and
Thelma J. O'Connell.

Accession No.

BUREAU OF RADIOLOGICAL HEALTH
RESEARCH GRANTS PROGRAM - FISCAL
YEAR 1972 (May 1973)

U.S. Department of Health, Education, and Welfare, PHS,
FDA, Bureau of Radiological Health - DHEW Publication
(FDA) 73-8038 (May 1973) 201 pp. (limited distribution).

ABSTRACT: The research grant activities described in this publication are funded by the Bureau of Radiological Health, Food and Drug Administration, and administered by the Bureau's Program Office. The aim of research grants is to support the Bureau's efforts to promote the health of man by reducing the hazards from radiation, both ionizing and nonionizing.

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KEYWORDS: Research Grants; Principal Investigators; Grantee Institutions; Geographical Locations; DHEW Regions; and Regional Office Information.

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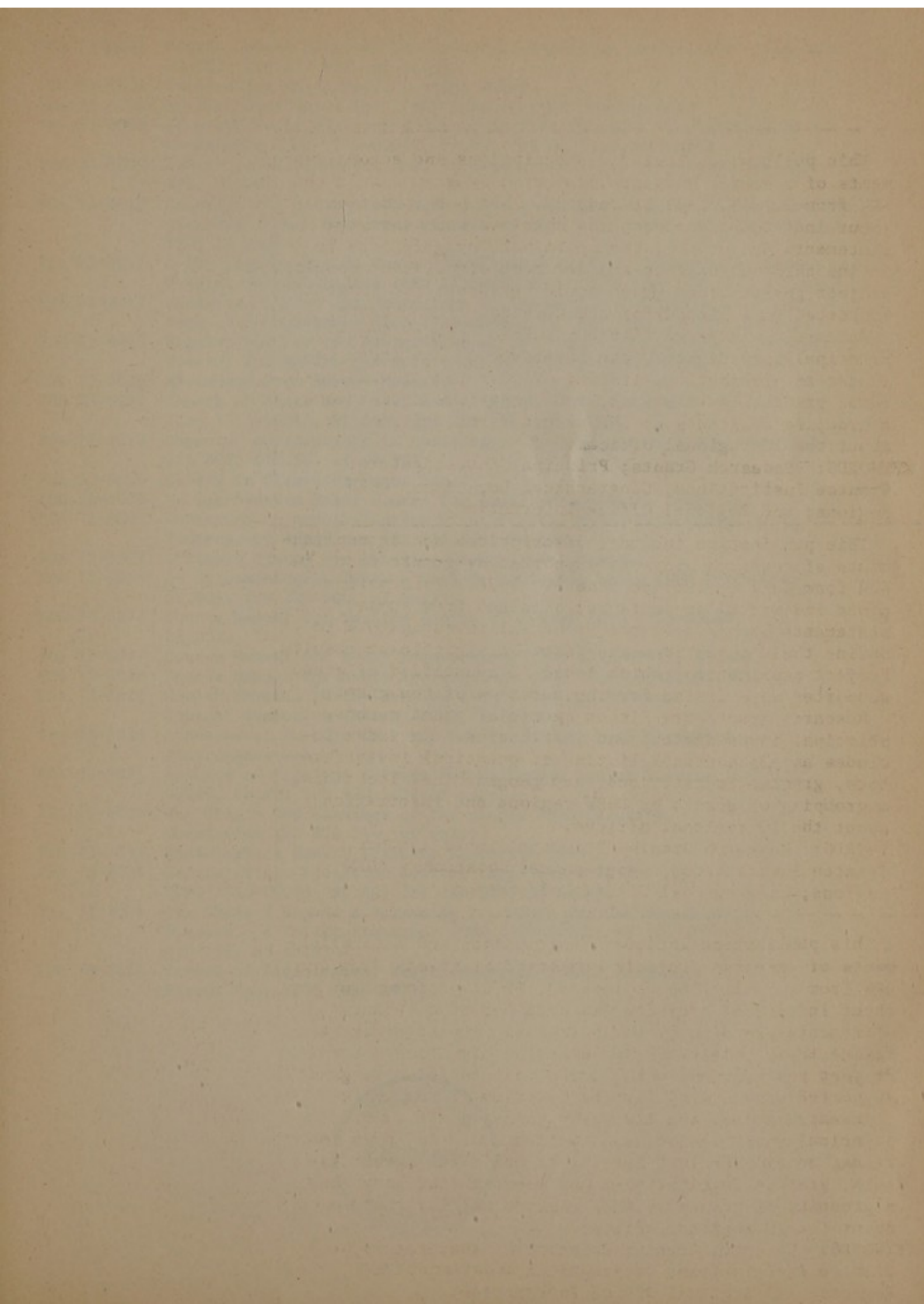
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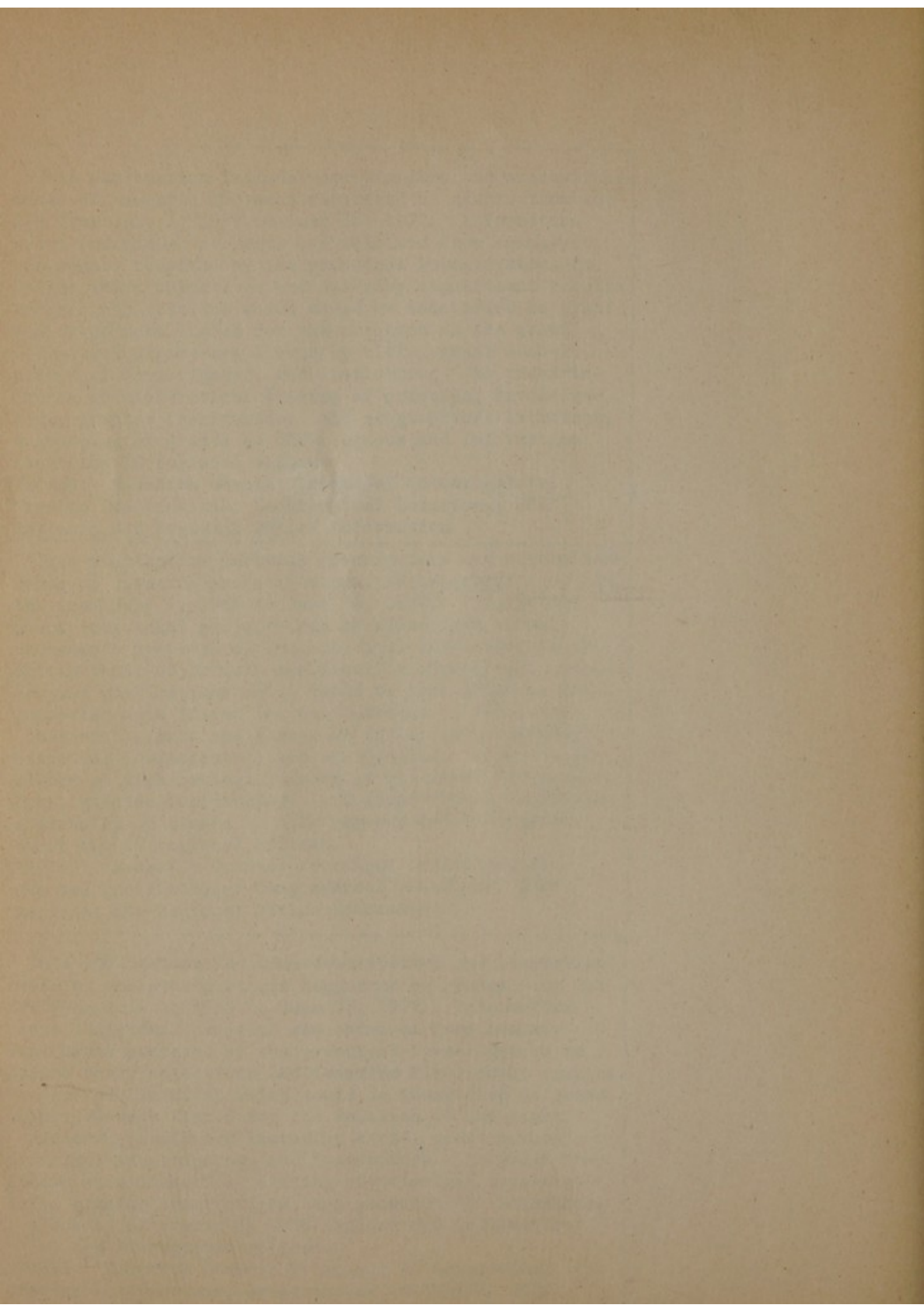
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FDA 73-8003 Fourth Annual National Conference on Radiation Control (GPO 1715-0038, \$3.50), (PB 212 531, mf only).
FDA 73-8004 Integrating Milliampere-Seconds Meter.
FDA 73-8005 An Insulated Meter for X-ray Tube Current Measurement.
FDA 73-8008 Interaction of Ultrasound and Biological Tissues: Proceedings of a Conference (GPO 1715-00052, \$3.45) (PB 220 143, mf only).
FDA 73-8009 Reduction of Radiation Dose in Diagnostic X-ray Procedures (PB 212 491, \$3.00).
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FDA 73-8027 Course Manual for X-Ray Measurements (GPO 1715-00047, \$5.10).
FDA 73-8028 Course Manual for X-Ray Applications (GPO 1715-00046, \$3.35).
FDA 73-8029 Health Physics in the Healing Arts - Seventh Midyear Topical Symposium (March 1973) (in press).
FDA 73-8030 A Review of In-Line RF Power Meters for Use With Ultrasonic Instrumentation.
FDA 73-8031 Results of Clinical Surveys for Microwave Ocular Effects (GPO 1715-00049, \$0.40) (PB 220 145, mf only).
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FDA 73-8038 Bureau of Radiological Health Research Grants Program, Fiscal Year 1972 (May 1973).



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