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Medical Department

DIVISION OF EXPERIMENTAL PATHOLOGY

Carcinogenic Action of Graded Doses of Whole-Body Irradiation (6120, 6310)*

The major tumor that has been induced by whole-body irradiation in the lethal and sublethal range is a mammary tumor that varies in appearance from a fibroadenoma to an adenocarcinoma with a few fibrosarcomata. The 1-yr incidence of mammary tumors is dose dependent and extrapolates back to approximately zero dose. The mechanism of induction appears to be indirect and requires the presence of a functioning ovary, but the latter need not be irradiated.

The tumors are in part transplantable. Both autonomous and hormone-dependent tumors exist. The rapidly growing autonomous tumor is clearly a carcinoma. Some tumors are metastasizing upon transplantation.

It may be possible in the near future to provide both autonomous and hormone-dependent mammary tumors for cancer chemotherapy testing programs. V.P. BOND, R.A. CONARD, E.P. CRONKITE, J. FURTH,** AND S.W. LIPPINCOTT

Metabolism of Co⁶⁰-Labeled Vitamin B₁₂ in Animals and Patients (6120)

Studies on the distribution and excretion of Co⁶⁰-labeled B₁₂ in dogs and other animals have been completed and reports are being prepared. Further work on plasma clearance and excretion of labeled B₁₂ in various blood dyscrasias and "normal" controls has been completed. Plasma concentration curves of Co⁶⁰ after the intravenous injection of the labeled B₁₂ show a periodic and an aperiodic component, which indicates that clearance is progressing simultaneously with mixing. The aperiodic portion consists of a fast and a slow component. Curve analyses are under way. Urinary and fecal excretion show two clear components, one with a half-time of 2½ days and the

other with a half-time of more than 300 days. The earlier suggestion of fast and slow plasma clearances in various blood dyscrasias must be reconsidered in view of the difficulty of curve analysis in the presence of simultaneous mixing and clearance.

E.P. CRONKITE, E. HENLEY,* L.M. MEYER,**
J.R. RUBINI, D.A. WILLIGAN, AND W. WOLINS

Radioautograph Studies of Cell Proliferation in Animals Utilizing Tritium-Labeled Thymidine (6120)

Tritium-labeled thymidine, developed by W.J. Hughes of this Department, has proved to be most effective in labeling the desoxyribonucleic acid (DNA) of proliferating tissues of the mouse. These studies are being made in collaboration with the BNL Biology Department and the National Institutes of Health (G. Brecher). To date the appearance and disappearance of labeled blood cells in the peripheral blood following single injections of labeled thymidine have been followed, as has their appearance in all tissues throughout the body as a function of time. In addition transfusion of labeled leukocytes has been accomplished and promises to be useful in studying the life span and fate of leukocytes. To date it appears that this agent will be most helpful in unraveling various time features of the generative cycle (intermitosis and mitosis).

V.P. BOND, R.A. CONARD, E.P. CRONKITE,
W.L. HUGHES, R. PAINTER,
AND H. QUASTLER†

Combined Effects of Beta Irradiation of the Skin and Whole-Body X-Irradiation on Carcinogenesis in the Skin (6310)

The possible additive effects of whole-body radiation and localized beta radiation of the skin in regard to carcinogenesis of the skin have not

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Explanation of these numbers, see Foreword.
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been determined. The problem is of both theoretical and practical interest, since the Marshallese people who were accidentally irradiated with fallout developed beta lesions of the skin and received a substantial dose of whole-body irradiation.

Groups of 50 female mice have been given 20,000 rep of beta radiation from a Sr^{90} source (750 rep/min) to a flap of skin on the back (area = 0.9 cm^2). Other groups of 50 mice have been given the same beta doses to the skin plus 400 r of whole-body x-irradiation. Still other groups of 50 mice were given 6000 rep of beta radiation to the skin, and corresponding groups received the same beta doses to the skin plus 400 r of whole-body irradiation. Another group of mice have received only a whole-body dose of 400-r x-radiation. Preliminary results indicate that in the 6000-rep group which received in addition 400 r of whole-body x-irradiation there was more skin damage at the site of the beta irradiation than in the group receiving the 6000 rep alone to the skin. A few malignant skin tumors are appearing which have been verified by histological study. The incidence of such tumors in the various groups will be determined in the near future.

R.A. CONARD, E.P. CRONKITE, AND V.P. BOND

Studies on the Toxicity of Irradiated Intestine

(6120)

The intestinal syndrome produced by supralethal doses of ionizing radiation is associated with 3- to 5-day deaths in most animals. The syndrome is characterized by extreme toxicity which seems greater than would be accounted for on the basis of fluid and electrolyte imbalance alone. The present studies were undertaken to determine whether any toxic agent (or agents) which might contribute to the syndrome is present in the irradiated intestine.

Many experimental approaches have been tried with, for the most part, negative results. Early toxicity of mucosal scrapings from unirradiated mice when injected intraperitoneally was found to be due largely to sepsis. Lethality from intravenous injections (very small amounts) is thought to be due to potassium toxicity.

Attempts are being made to determine toxicity by a more normal route of injection such as directly into the intestines of irradiated mice. Studies are under way on the influence of an increase in body levels of potassium and sodium (by

addition of the elements to the drinking water) on the survival time in the acute intestinal syndrome. An attempt is also being made to protect irradiated mice from the intestinal syndrome by intraluminal injections of normal mucosal cells into the small intestine in the hope of producing seeding.

R.A. CONARD AND H. QUASTL

Studies on the Marshallese People Exposed to Fallout Radiation

(660)

The annual expedition to the Marshall Islands: the medical examination of the 82 Marshallese people exposed to significant fallout radiation in 1957 was carried out in March 1957, three years after exposure. The findings of this survey will be published in a joint BNL - Naval Medical Research Institute report. Preparations are being made for a four-year survey in March 1958. Hematology and other examinations are contemplated for the next survey, which will be made at Rongerik where these people now live. In addition, it is hoped that a whole-body gamma analyzer will be set up aboard a Navy LST for the purpose of carrying out gamma spectrographic analyses on both exposed and unexposed people on Rongerik. These will be correlated with urinary excretion rates of isotopes. As in the past, the United States Navy is assisting the Atomic Energy Commission, Brookhaven National Laboratory, and agents of the Department of Defense in this survey.

R.A. CONARD, B. CANNON,* COL. A. LOWE,
J.E. RALL,† LT. COL. S. BAUMANN,
L. MEYER, AND E. CAHILL

Studies on the Therapeutic Efficacy of an Aloe vera Extract in Beta Lesions of the Skin

(6)

The therapeutic efficacy of local daily application of an *Aloe vera* plant extract to acute burns of the skin of mice and rats is being investigated. Results are inconclusive at this time. The extract (furnished by Forkas Chemical Corporation) is said to be of benefit in the healing of the burns.

R.A. C

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†Research collaborator from National Institutes of Health, Bethesda, Md.

Pathology of Particle Radiation (6310)

Studies are being carried out on the pathological effects of thermal neutrons and of the heavy particles from the $B^{10}(n,\alpha)Li^7$ reaction on the skin of pigs. S.W. LIPPINCOTT, V.P. BOND, J.S. ROBERTSON AND E.P. CRONKITE

Clinical Studies of Labeled Protein Fractions (6310, 6320)

Clinical studies of labeled protein fractions are being carried out on normal individuals, patients with miscellaneous diseases, and patients with various types of carcinoma, as a possible diagnostic aid in detecting early cancer.

S.W. LIPPINCOTT, W.L. HUGHES, W. WOLINS, AND C.T.O. FONG

Function, Fate, and Control of Platelets (6120)

High levels of a physiologically active substance, serotonin, are found in blood platelets and parts of the gastrointestinal tract. Serotonin levels of tissues and platelets will be measured colorimetrically from tissues of normal and irradiated animals and platelet preparations to assess further the role of this substance in radiation injury and the effectiveness of platelet preparations in controlling radiation hemorrhage.

Urine levels of 5-hydroxyindoleacetic acid, the secreted metabolite of serotonin, will be measured in normals, leukemics, and other blood dyscrasias.

In addition, the comparative effectiveness of fresh and lyophilized platelets in the control of radiation bleeding will be evaluated.

V.P. BOND, R.A. CONARD, E.P. CRONKITE, J. RUBINI, AND D. SORENSEN

Papers Presented

FIRST INTERNATIONAL CONGRESS
OF NEUROLOGICAL SCIENCES,
BRUSSELS, JULY 1957

The Neuropathological and Topographical Study of Whole Brains Following Neutron Capture Therapy in Glioblastoma Multiforme. L.E. Farr, S.W. Lippincott, W. Kahle, P. Yakovlev,* and W. Haymaker.**

FIRST PAN-AMERICAN CANCER
CYTOLOGY CONGRESS,
MIAMI, APRIL 1957

Studies on Tissues of Animals Receiving Sulfur-Labeled Platelet Transfusions. E.P. Cronkite.

AMA FIFTH ANNUAL NATIONAL CIVIL
DEFENSE CONFERENCE,
NEW YORK, JUNE 1957

The Effects of Total-Body Exposure to Ionizing Radiation on Human Beings - Fallout Problems and Civil Defense. E.P. Cronkite.

*Research collaborator from Harvard Medical School, Boston, Mass.

**Research collaborator from Armed Forces Institute of Pathology, Washington, D.C.

Publications

Prepared statement on Somatic Effects, testimony before Joint Committee on Atomic Energy, Congress of the U.S., June 3, 1957, at the open hearings on The Nature of Radioactive Fallout and Its Effects on Man. E.P. Cronkite. *Congressional Record*, September 1957.

Fallout, Civil Defense and Effects of Radiation on Man. E.P. Cronkite. *J. Am. Veterinary Med. Assoc.*, in press.

The Use of Platelet Transfusions in Hemorrhagic Disease. E.P. Cronkite and D.P. Jackson.* Chapter in *Progress in Hematology*, Grune and Stratton, New York, 1957.

Gastric Lesions in Experimental Animals Following Single Exposures to Ionizing Radiations. G. Brecher,** E.P. Cronkite, R.A. Conard, and W.W. Smith.† *Am. J. Pathol.*, in press.

Acute Whole-Body Radiation Injury: Pathogenesis, Pre- and Postradiation Protection. V.P. Bond, E.P. Cronkite, and R.A. Conard. *Atomic Medicine*, in press.

The Diagnosis and Therapy of Acute Radiation Injury. E.P. Cronkite, V.P. Bond, and R.A. Conard. *Atomic Medicine*, in press.

The Hematology of Ionizing Radiation. E.P. Cronkite, V.P. Bond, and R.A. Conard. *Atomic Medicine*, in press.

Fallout Radiation: Effects on the Skin. R.A. Conard, E.P. Cronkite, and V.P. Bond. *Atomic Medicine*, in press.

Human Radiation Injury Diagnosis, Therapy and Prognosis. E.P. Cronkite. *Proc. 6th Intern. Congr. Hematol.* (Boston), 1957.

*Research collaborator from the Johns Hopkins University School of Medicine and Hospital, Baltimore, Md.

**Research collaborator from National Institutes of Health, Bethesda, Md.

†National Institutes of Health, Bethesda, Md.

DIVISION OF MICROBIOLOGY

The Sites of Catabolism of Plasma Albumin (6120)

In an extension of the study reported a year ago (W.L. Hughes, *Proc. 8th Ann. Conf. Natl. Nephrosis Found.*, 1956, p. 22) on the effect of nephrectomy on the catabolic rate of labeled plasma albumin, the

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effect of removing the intestines or large portions of the liver has been investigated. Removal of the intestines had no effect, but removal of portions of the liver decreased the rate of catabolism in proportion to the amount of liver removed. This effect can be much greater than that seen following nephrectomy and suggests that the liver must be the major site of catabolism for plasma albumin.

D. GITLIN,* J.R. KLINENBERG,**
G. TERRES, AND W.L. HUGHES

Catabolism of Serum Albumins in Mice (6120)

The comparison of data obtained in this laboratory for the half-life of crystalline bovine serum albumin (BSA) with the data for human serum albumin (HSA) reported by Melcher et al. [*J. Immunol.* 71, 275 (1953)] shows nearly a twofold difference. These investigators, using iodinated HSA and following the catabolic rate by serum sampling, have found a half-life of 1.5 days. At BNL, by using whole-mouse counting, the biological half-life for iodinated BSA has been found to be between 0.6 and 0.7 days. Although it would be surprising if mice could distinguish between HSA and BSA to the extent noted (short of an immune response), various preparations of HSA (crystalline, fraction V, and commercially prepared RISA) were tested in BNL mice with whole-body counting. The results indicated no significant difference in half-lives between the different HSA preparations; they had half-lives of 0.75 days, slightly longer than those for BSA. Further studies in which the catabolic rate was determined both by whole-mouse counting and by serum sampling ruled out the possibility of differences based on methods of determination. Since it is felt that Melcher's group has reported an accurate value, and that the results obtained at BNL also merit confidence, the present line of investigation is being continued in an attempt to resolve this discrepancy. The approach now being followed is one of testing various strains of mice. G. TERRES AND W. WOLINS

An Investigation of the Induction of Acquired Tolerance to Crystalline Bovine Serum Albumin in Mice (6120)

To date all work with mice on acquired toler-

homotransplantation resulting from prenatal exposure of the same homologous tissue. This procedure was unsatisfactory for studies in which large numbers of animals were desired, since a high mortality rate occurred. Recently Billingham and Brent [*Proc. Roy. Soc. (London)* B146, 78 (1956)] have reported a higher occurrence of tolerance in animals when the inducing exposure is made at birth and intravenously. The work with tolerance still has the disadvantage of involving a heterogeneous mixture of antigens, with each antigen establishing its own state of tolerance in accordance with its own essential characteristic properties. As a step toward the elucidation of the mechanism underlying tolerance, a system employing a pure antigen and capable of easily producing a state of tolerance in a large number of animals seemed highly desirable.

Crystalline bovine serum albumin (BSA) was chosen as the antigen to be tested, and postnatal injection as a possible method of induction. The initial injections of BSA (12.5 mg in 0.05 ml) were made intraperitoneally. Very few mice were lost as a result of the method of injection. This procedure was tested in single and multiple exposures at various periods after birth. Animals so exposed were later given a series of sensitizing injections to test for the establishment of tolerance. The procedure of sensitization was such as to produce fatal anaphylaxis in 40 to 75% of control mice.

The most successful experiment resulted from initial exposure to 4 injections starting at birth or at 1 wk of age and administered on a 1-3-6-8-day schedule. The mice were tested for tolerance at 6 wk; none of the treated mice showed any signs of shock, while the controls (litter mates) showed approximately 40% fatalities. The same procedure was tested when the mice were 11 and 17 wk of age. Fatal shock was recorded in the treated animals, but less frequently than in the controls, which indicated a transient characteristic. Animals given a single exposure also showed less anaphylaxis than the controls, but the differences were less significant.

Postnatal exposure to greater amounts of BSA produced an effect even when the mice were 6 mo of age. The amount used per injection in the post-