V. LIST OF ATTENDEES

AD HOC STUDY GROUP MEETING, MAY 28 AND 29, 1968

ON

A STUDY OF EARLY RADIATION-INDUCED BIOLOGICAL CHANGES AS INDICATORS OF RADIATION INJURY

CO-CHAIRMEN

C. Jelleff Carr, Ph.D.
Director, Life Sciences
Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

M. Ingram, M.D.
Associate Professor
Department of Radiation Biology
and Biophysics
School of Medicine and Dentistry
University of Rochester
Rochester, New York 14620

PARTICIPANTS

Gould A. Andrews, M.D.
Director, Medical Division
Oak Ridge Associated
Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Michael A. Bender, Ph.D.
Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Siegmund J. Baum, Ph.D.
Chairman, Experimental
Pathology Department
Armed Forces Radiobiology
Research Institute
Defense Atomic Support Agency
National Naval Medical Center
Bethesda, Maryland 20014

Colonel Louis E. Browning, MC
Deputy Director
Armed Forces Radiobiology
Research Institute
Defense Atomic Support Agency
National Naval Medical Center
Bethesda, Maryland 20014

Eugene P. Cronkite, M.D.
Chairman, Medical Department
Brookhaven National Laboratory
Upton, Long Island
New York 11973

Colonel Jack C. Fitzpatrick, MC
Surgeon, Field Command (FCSG)
Defense Atomic Support Agency
Sandia Base
Albuquerque, New Mexico 87115

Kenneth P. DuBois, Ph.D.
Professor of Pharmacology
Department of Pharmacology
School of Medicine
University of Chicago
Chicago, Illinois 60637

Tyron E. Huber, M.D.
Director, Office of Biomedical Studies
Federation of American Societie for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Arthur J. Emery, Jr., Ph.D.
Life Sciences Division
Army Research Office
Office of the Chief of Research and Development
3045 Columbia Pike
Arlington, Virginia 22204

James Edward Huff, Ph.D.
Research Associate
Life Sciences Research Office
Federation of American Societie for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Adelbert S. Evans
Radiation Biology Department
Armed Forces Radiobiology Research Institute
Defense Atomic Support Agency
National Naval Medical Center
Bethesda, Maryland 20014

LTC Merrill C. Johnson, MC
Chief, Department of Radiation Biology
Walter Reed Army Institute of Research
Walter Reed Army Medical Cente
Washington, D. C. 20012

Kenneth D. Fisher, Ph.D.
Research Associate
Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Robert F. Kallman, Ph.D.
Department of Radiology
Stanford University
School of Medicine
300 Pasteur Drive
Palo Alto, California 94304

John B. Little, M.D.
Assistant Professor of
Radiobiology
Department of Physiology
Harvard School of Public Health
Boston, Massachusetts 02115

David Sturrock, M.D.
Wing Commander, Royal Air Force
Radiobiology Division
Brooks Air Force Base
San Antonio, Texas 78235

LTC Dorsey T. Mahin, MC
Director, Division of Nuclear
Medicine
Walter Reed Army Institute of
Research
Walter Reed Army Medical Center
Washington, D. C. 20012

C.M. Unruh
Technical Staff
Environmental and Life Sciences
Battelle Memorial Institute
Pacific Northwest Laboratory
P. O. Box 999
Richland, Washington 99352

J.F.A. McManus, M.D.
Executive Director
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Alvin Volkman, M.D., D. Phil.
Assistant Member
Trudeau Institute
Algonquin Avenue
Saranac Lake, New York 12983

Seymour M. Perry, M.D.
Associate Scientific Director
of Clinical Trials
Room 6B17, Building 10
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

Niel Wald, M.D.
Professor of Radiation Health, and
Director, Radiation Health Division
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

Eugene L. Saenger, M.D.
Director, Radioisotope
Laboratory
Cincinnati General Hospital
Cincinnati, Ohio 45229

Richard A. Weiss, Ph.D.
Deputy and Scientific Director
of Army Research
Army Research Office
Office of the Chief of Research
and Development
3045 Columbia Pike
Arlington, Virginia 22204

EX OFFICIO PARTICIPANTS

Colonel Kenneth Dirks, MC
Chief, Research Division
U.S. Army Medical Research and Development Command
Office of The Surgeon General
Main Navy Building, Room 2612
Washington, D. C. 20315

Major Charles E. White, MSC
Operations and Policy Branch
Nuclear, Biological and Chemical Sciences Division
U.S. Army Medical Research and Development Command
Office of The Surgeon General
Main Navy Building, Room 1713
Washington, D. C. 20315

Major William E. Woodward, MSC
Research Branch
Nuclear, Biological and Chemical Sciences Division
U.S. Army Medical Research and Development Command
Office of The Surgeon General
Main Navy Building, Room 1711
Washington, D. C. 20315

D. CHANGES IN URINARY CONSTITUENTS

Among the urinary constituents that have been identified from irradiated animals and man are certain amino acids, β-aminoisobutyric acid, creatine, and taurine; pyrimidine deoxyribosides, deoxycytidine and thymidine; cyclic and heterocyclic biogenic amines; and 5-hydroxyindoleacetic acid.

Excretion of deoxycytidine (CdR) in the urine of rats exposed to radiation has been extensively studied. For example, Kereiakes and associates (24) reported that the increased level of CdR in the 24-hour post-irradiation urine exhibited first order kinetics up to 200 R. The peak of CdR excretion was approximately 15 hours post-irradiation returning to pre-irradiation values at 24 hours.

In measuring the urinary excretion levels of human cancer patients receiving whole-body doses of ^{60}Co radiation, it was found (25) that CdR was excreted in the post-irradiation urine, whereas lower levels of CdR could be detected in the urine collected before irradiation. Elevated urinary levels of CdR may not be specific for radiation injury because similar observations have been made on patients with various stresses such as burns. A notable advance has been the development (26) of a more sensitive (1.0 μg CdR/10 ml urine) and rapid method for the detection and isolation of urinary CdR that utilizes successive exchange resin chromatography.

Increases (25-50%) in plasma CdR in rats following low doses of X-rays (< 50R) suggested that the quantitative determination of CdR might be an indicator of radiation injury (27). A dose-response relationship was found in the range of 50 to 200 R. However, an increase in urinary excretion of various pyrimidine derivatives has been found and there is a possibility that the elevated CdR levels may result from an increased synthesis of pyrimidines (28). Radiation may affect the control mechanism responsible for pyrimidine metabolism and the observed changes could then be related to this action.

Alterations in the excretion patterns of fluorescent urine products by rodents and nonhuman primates were reported (29) after whole-body sublethal ^{60}Co irradiation exposure. The measurements can be made accurately and rapidly 2 to 36 hours post-irradiation. The effects of irradiation injury to the rats were reflected by increased urinary excretion of certain fluorescent products, urinary phosphorus, and the urine volume. The increased phosphorus excretion rates for primates after irradiation appear directly related to the dose while the total fluorescent changes may not be dose-related.

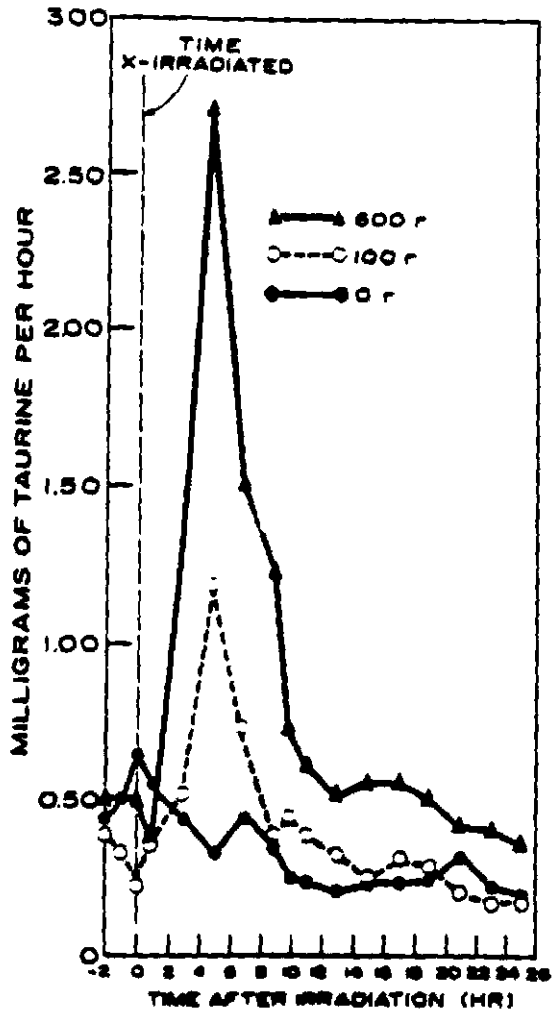
Creatinuria has been observed in animals following exposure to radiation. The radiation-induced creatinuria results from a failure of muscle tissue to utilize creatine synthesized at a normal rate (30). No alterations in rate of creatine synthesis or in its release from muscle were observed after irradiation. The creatinuria is dose dependent and is maximal between 2 and 4 days after a single whole-body exposure. Koszalka and Andrew (31) reported that insulin completely suppressed creatinuria in rats irradiated with a dose of 500 rad. This phenomenon may extend to other drugs and should be studied.

Excessive urinary excretion of taurine has been observed in the rat after whole-body irradiation. There is an increase in taurine excretion with increasing dose, up to 250 R, but above 250 R the amount of excess taurine excreted by the rat is independent of the dose and, in addition, the bulk of the excess taurine is excreted within 8 hours (32). The hourly urinary excretion of taurine after a single dose of whole-body irradiation is shown in Figure 1. Evidence has been presented that the irradiated rat gives rise to a limited excretion of taurine. A second radiation exposure within approximately 7 days following a maximal response does not elicit a similar excretion of taurine (33). Therefore, this index of radiation injury could be used only if single acute doses of radiation were suspected. The presence of the pancreas is necessary for increased excretion of taurine post-irradiation, whereas the presence of the spleen, adrenals, kidneys, and hypophysis is not required.

Animal data, although useful, are by no means directly applicable to man (34). In man, urinary biochemical indicators of radiation injury have proved disappointing. The studies reported after radiation accidents or therapy have not shown good correlations between these urinary constituents and the degree of radiation injury. Wide individual variation in human urinary constituents and the difficulty in quantitatively collecting urine samples further complicate the use of these indicators as measures of radiation injury in the soldier. More extensive study of the changes in urinary products induced by radiation is necessary before meaningful indices can be developed.

(See Section VII, Suggested Areas for Future Research, p 62)

Figure 1



Hourly urinary excretion of taurine after a single dose of whole-body X-irradiation. Minus number on the time scale indicates hours prior to irradiation. Each value is the average of 3 rats (Ref. 33).

H. TOTAL PROTEIN-BOUND NEUTRAL HEXOSES

Serum glycoproteins have been reported to be increased in a number of infectious, inflammatory, neoplastic, and idiopathic diseases. The significance of these changes is not known, and there is evidence that different disease states produce more or less distinctive alterations in the relative concentration of various carbohydrate species bound to protein (53).

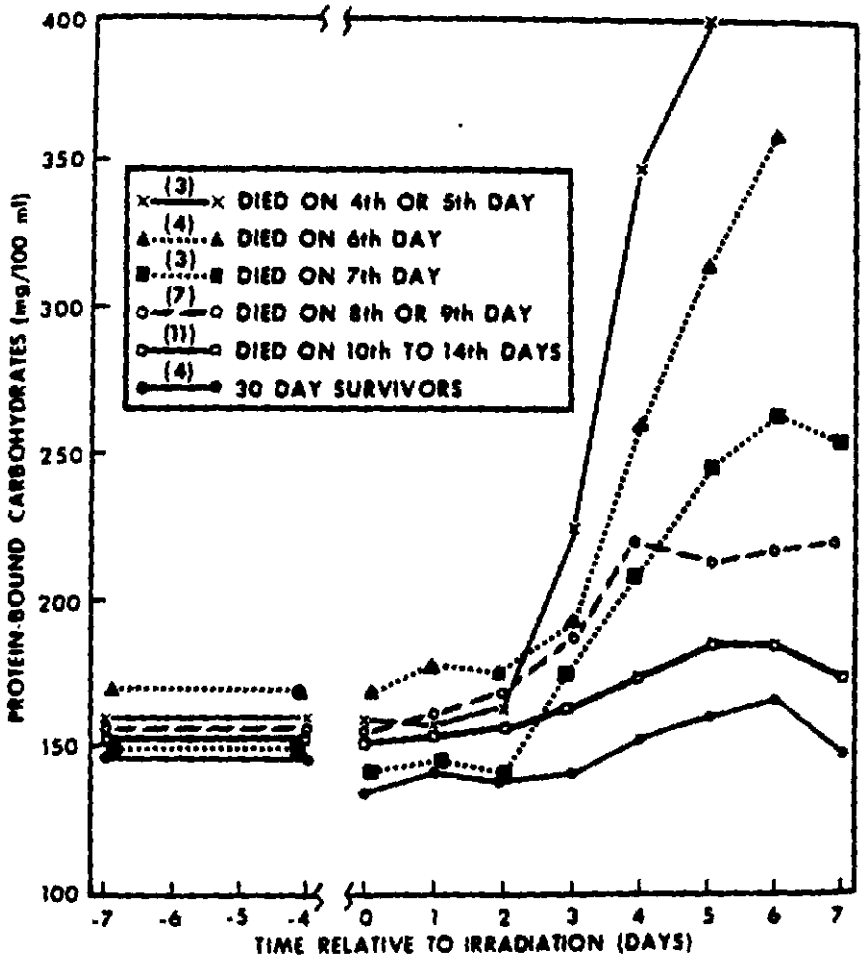
Evans and colleagues studied the effects of ionizing radiations on the concentration and distribution of protein-bound carbohydrates (PBC) in the plasma of mice (54) and beagles (9). The PBC were estimated as neutral hexoses in the plasma during the pre- and post-irradiation period, and the changes observed were related to the survival time of the animals.

The plasma PBC values in C_3H mice and beagles were determined before and after whole-body exposures of monoenergetic 14 MeV neutrons or mixed gamma-neutron radiations. The mice were exposed to both sources at a steady state rate of ≈ 20 rad/min. The beagles received pulsed doses of mixed gamma-neutron radiations. In both species, the pre- and post-irradiation PBC appeared to constitute a crude index of radiosensitivity prior to, and prognosis after, irradiation in these otherwise healthy animals.

A striking difference was observed between the mice (Figure 9) and dogs (Figure 10) that died after exposure to mixed gamma-neutron radiations and the more resistant animals that, although exposed to identical doses, survived the experimental period. In the animals that died, the PBC rose to varying degrees and remained elevated until their death. By contrast, the survivors demonstrated little change in PBC, deviating only slightly from their pre-irradiation baseline values. There was an inverse relationship between the magnitude of maximum response and the survival time of the animals. Similar results have been reported for dogs receiving whole-body radiation doses of 600 R (55). Dogs with a low initial level of glycoproteins generally survived 30 days after exposure. animals with high initial levels died.

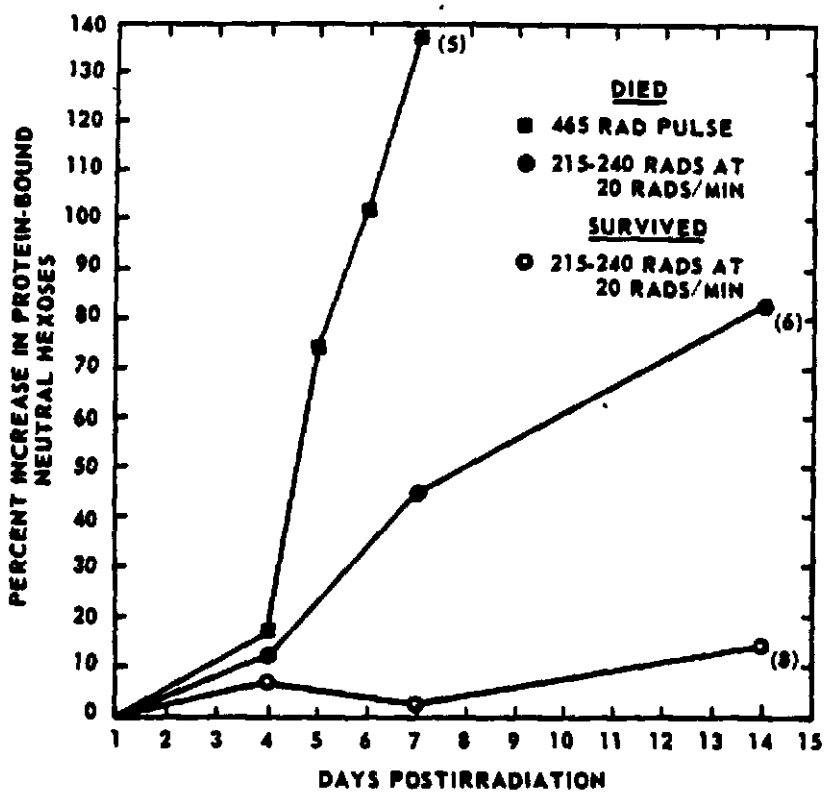
It was noted that the mean pre-irradiation level of PBC of the 30-day survivors was lower than those that died during the same period (Table 1). The pre-irradiation PBC concentration indicated statistically significant differences in radiosensitivity at the lowest reported dose. This finding together with the inverse relationship between radiation dose and magnitude of difference was

Figure 9



Protein-bound carbohydrates as neutral hexoses in the plasma of mice as a function of time relative to exposure to 455 rad of mixed gamma-neutron radiations. Numbers in parentheses are number of mice represented by each curve (Courtesy Adelbert S. Evans; Ref. 54).

Figure 10



Percent increase in concentration of total neutral hexoses in the plasma of dogs at indicated times after exposure to mixed gamma-neutron radiations. Numbers in parentheses are number of animals represented by each curve (Courtesy Adelbert S. Evans).

Table 1

COMPARISON OF PREIRRADIATION PROTEIN-BOUND CARBOHYDRATE (PBC) CONCENTRATION IN MICE WHICH DIED WITH THE 30-DAY SURVIVORS AFTER EXPOSURE TO 14-MEV NEUTRONS OR MIXED GAMMA-NEUTRON RADIATIONS

	14-MeV neutrons				*Mixed gamma-neutron radiations*			
	365 rads		*450 rads*		*455 rads*		*515 rads*	
	Died	*Survived*	*Died*	*Survived*	*Died*	*Survived*	*Died*	*Survived*
Number of Mice	5	9	6	4	28	4	48	2
Mean PBC ±	170.6	151.6	167.0	149.5	156.1	145.5	160.0	152.5
S.E.[a]	± 3.4	± 2.9	± 5.8	± 6.8	± 2.5	± 5.6	± 2.0	--
Δ[b]	19.0		17.5		10.6		7.5	
p	< 0.01		0.05 < *p* < 0.1		0.1 < *p* < 0.2		0.4 ± *p* ● 0.5	

a Milligrams per 100 ml of plasma.
b Δ = died minus survived.

(Courtesy Adelbert S. Evans; Ref. 54).

that this subject is worthy of further investigation. In another series of 27 beagles that received a pulsed dose of 215 rad of mixed gamma-neutron radiations, the mean pre-irradiation PBC concentration of the 13 beagles that survived was lower than that of the 14 that died. Causal relation between the pre-irradiation PBC values and radiosensitivity is not known but it may be a reflection of an inherent metabolic lesion in the sensitive animals that renders them less tolerant to a radiation insult.

Admittedly, the estimation of the structurally and physiologically widely diverse glycoproteins as a single entity cannot be expected to yield clinically applicable criteria. However, Evans (9) has found by preparative fractionation of plasma of irradiated and unirradiated animals, that absolute changes occur in the concentration of transferrin, haptoglobulins, β_2-glycoproteins, and α_2-macroglobulin. These proteins are all rich in bound carbohydrates.

Preliminary analyses of the whole plasma of beagles for radiation-induced alterations in the various carbohydrate species bound to protein - neutral hexoses (as galactose and mannose), hexosamines (as glucosamine), sialic acid (as N-acetylneuraminic acid), and methyl pentose (as fucose) - revealed that the relative alterations of these carbohydrates are distinctive and do not mimic the reported values for hypertensive heart disease, myocardial infarction, or liver disorders. In addition, ultrastructural changes in intracellular organelles thought to be vital in the biosynthesis of complex proteins that parallel the biochemical findings have been shown in the hepatocytes of irradiated mice (9).

Continuation of these studies on protein-bound carbohydrates should give a better understanding of the mechanism of radiation injury. It appears feasible to explore the estimation of particular protein-bound carbohydrates as a prognostic test to aid in following the clinical course of an irradiated individual, and to identify the most radiosensitive individuals prior to possible radiation exposure.

(See Section VII, Suggested Areas for Future Research, p 63)

8. Nygaard, O.F., and Potter, R.L.
Effect of X-Radiation on DNA Metabolism in Various Tissues of the Rat. 1. Incorporation of C^{14}-Thymidine into DNA During the first 24 Hours Post-irradiation.
Rad. Res. 10: 462-476 (1959).

9. Evans, A.S.
Effects of Ionizing Radiations on the Concentration and Distribution of Protein-Bound Carbohydrates in the Plasma of Mice and Dogs.
Abstract in: DASA Conference Program, DASA Conf. at U.S. Naval Radiobiological Defense Lab., San Francisco, California (9-11 April, 1968).

10. Bender, M.A.
X-Ray-Induced Chromosome Aberrations in Mammalian Cells In Vivo and In Vitro.
Int. J. Rad. Biol. Suppl. 103-108 (1960).

11. Vogel, J.M., Yankee, R.A., Kimball, H.R., Wolff, S.M., and Perry, S.
The Effect of Etiocholanolone on Granulocyte Kinetics.
Blood 30: 474-484 (1967).

12. Wolff, S.M., Kimball, H.R., Perry, S., Root, R., and Kappas, A.
The Biological Properties of Etiocholanolone.
Combined Clinical Staff Conference at the National Institutes of Health.
Ann. Intern. Med. 67: 1268-1295 (1967).

13. Vogel, J.M., Kimball, H.R., Foley, H.T., Wolff, S.M., and Perry, S.
Effect of Extensive Radiotherapy on the Marrow Granulocyte Reserves of Patients with Hodgkin's Disease.
Cancer 21: 798-804 (1968).

14. Cameron, J.R., Suntharalingam, N., and Kenney, G.N.
Thermoluminescent Dosimetry.
The University of Wisconsin Press, Madison, Wisconsin, 232 p (1968).

15. Becker, K.
Recent Progress in Radiophotoluminescence Dosimetry.
Health Phys. 14: 17-32 (1968).

16. Borison , H.L., and Wang, S.C.
Physiology and Pharmacology of Vomiting.
Pharmacol. Rev. 5: 193-230 (1953).

17. Chinn, H.I., and Wang, S.C.
Locus of Emetic Action Following Irradiation.
Proc. Soc. Exp. Biol. Med. 85: 472-474 (1954).

18. Borison, H.L.
Site of Emetic Action of X-Radiation in the Cat.
J. Comp. Neurol. 107: 439-453 (1957).

19. Wang, S.C., Renzi, A.A., and Chinn, H.I.
Mechanism of Emesis Following X-Irradiation.
Amer. J. Physiol. 193: 335-339 (1958).

20. Chinn, H.I., and Sheldon, G.I.
Effect of Chlorpromazine on Emesis After Radiation.
Proc. Soc. Exp. Biol. Med. 86: 293-295 (1954).

21. Oakberg, E.F.
The Effect of Low Radiation Doses on Spermatogonia and Oocytes of the Mouse.
Strahlenwirkung und Milieu 51: 103-115 (1962).

22. Merz, T.
Radiation Injury. Chapter XVI.
In: Principles of Nuclear Medicine, Wagner, H.N., Ed.
W.B. Saunders Company, Philadelphia, pp 722-741 (1968).

23. Casarett, G.W., and Eddy, H.A.
Fractionation of Dose in Radiation-Induced Male Sterility.
In: Dose Rate in Mammalian Radiation Biology, Brown, D.G., Cragle, R.G., and Noonan, T.R., Eds., Conf. 680410, Biol. and Med. (TID-4500), USAEC Div. Tech. Inform. Ext., Oak Ridge, Tennessee, pp 14.1-14.10 (1968).

24. Kereiakes, J.G., Chen, I.W., Friedman, B.I., and Saenger, E.L.
Deoxycytidine Levels in Urine of Irradiated Cancer Patients and Rats.
Abstract in: DASA Conference Program, DASA Conf. at U.S. Naval Radiobiological Defense Lab., San Francisco, California (9-11 April, 1968).

25. Berry, H.K., Saenger, E.L., Perry, H., Friedman, B.I., Kereiakes, J.G., and Scheel, C.
Deoxycytidine in Urine of Humans After Whole Body Irradiation.
Science 142: 396-398 (1963).

26. Chen, I.W., Kereiakes, J.G., Friedman, B.I., and Saenger, E.L.
Colorimetric Analysis of Deoxycytidine in Urine After Separation by Ion Exchange Column Chromatography.
Anal. Biochem. 23: 230-240 (1968).

27. Guri, C.D., Swingle, K.F., Cole, L.J., and Bailey, J.S.
Elevated Plasma Deoxycytidine Levels in Rats: A Biological Dosimeter of X-Radiation.
U.S. Naval Radiological Defense Laboratory, San Francisco, USNRDL-TR-67-153. 24 p (1967).

28. Guri, C.D., and Cole, L.J.
Urinary Pyrimidines After X-Radiation.
U.S. Naval Radiological Defense Lab., San Francisco, USNRDL-TR-68-15. 24 p (1968).

29. Demetriou, J.A., and Beattie, J.M.
Fluorometric Detection of Biologic Changes in Irradiated Laboratory Animals.
USAF School of Aerospace Med. Div., Brooks AFB, Texas, SAM-TR-68-43. 23 p (1968).

30. Gerber, G.B., Gerber, G., and Altman, K.I.
The Mechanism of Radiation-Induced Creatinuria.
Proc. Soc. Exp. Biol. Med. 110: 797-799 (1962).

31. Koszalka, T.R., and Andrew, C.L.
Prevention of Radiation-Induced Creatinuria by Insulin.
Science 160: 1112-1113 (1968).

32. Kay, R.E., Early, J.C., and Entenman, C.
Increased Urinary Excretion of Taurine and Urea by Rats Following X-Irradiation.
Rad. Res. 6: 98-109 (1957).

33. Kay, R.E., and Entenman, C.
The Effect of Multiple Exposures and Partial Body X-Irradiation on Urinary Taurine Excretion by the Rat.
Rad. Res. 11: 357-369 (1959).

34. Zícha, B., and Buřič, L.
Deoxycytidine and Radiation Response: Exceedingly High Deoxycytidine Aminohydrolase Activity in Human Liver.
Science 163: 191-192 (1969).

54. Evans, A.S., Quinn, F.A., Brown, J.A., and Strike, T.A.
Effect of Ionizing Radiation on Total Protein-Bound Neutral Hexoses in the Plasma of Mice.
Rad. Res. 36: 128-137 (1968).

55. Zícha, B.
Radiation Effects on Serum Protein Changes in Peripheral Blood.
In: Experimentalalni Postiradiacni Syndrom. pp 75-84, Dienstvier, Z., Arient, M., Eds. Praha, Czechoslovakia, Statni Zdravotnicke Nakladatelstvi (1966) (In Czech) pp 75-84.
Abstract In: Life Sci. 7: 5297 (1968).

56. Hietbrink, B.E., and DuBois, K.P.
Influence of X-Radiation on Development of Enzymes Responsible for Desulfuration of an Organic Phosphorothioate and Reduction of p-Nitrobenzoic Acid in the Livers of Male Rats.
Rad. Res. 22: 598-605 (1964).

57. Davis, L.W., and Strike, T.A.
Effectiveness of Drugs in Animals Exposed to Mixed Gamma-Neutron Radiations. IV. Drug Toxicity.
Armed Forces Radiobiology Research Institute, Defense Atomic Support Agency, Bethesda, Maryland, AFRRI SR68-12, 18 p (1968).

58. Doull, J.
Pharmacological Responses in Irradiated Animals.
Rad. Res. 30: 333-341 (1967).

59. Hietbrink, B.E., and DuBois, K.P.
Influence of Partial-Body X-Irradiation on Development of Phosphorothioate Oxidase in the Livers of Male Rats.
Rad. Res. 27: 669-675 (1966).

60. DuBois, K.P.
Inhibition by Radiation of the Development of Drug Detoxification Enzymes.
Rad. Res. 30: 342-350 (1967).

61. Yam, K.M., and DuBois, K.P.
Effects of X-Irradiation on the Hexobarbital-Metabolizing Enzyme System of Rat Liver.
Rad. Res. 31: 315-326 (1967).

62. Nair, V., and Bau, D.
Inhibition of a Hepatic Microsomal Enzyme System After Head X-Irradiation of Rats.
Proc. Soc. Exp. Biol. Med. 126: 853-856 (1967).

intervals of two or three days, for a total of four, five or six doses. Urinary taurine levels were significantly increased following the single exposures to 450 R and 900 R, but not following 225 R. Increased taurine excretion was also observed (beginning on the fifth day after the first dose) in two of the four patients who received multiple 100 R doses. (Urine of five normal adult males was analyzed to establish normal values for comparison.) The authors comment that, "The source of taurine which is excreted in excess after radiation exposure is not known."

76. Harris, H.
Family Studies on the Urinary Excretion of β-aminoisobutyric Acid.
Ann. Eugenics 18: 43 (1954).

Paper chromatographic methods were applied in estimating the amount of β-aminoisobutyric acid (BAIBA) in 24 hour urine specimens of 345 normal individuals representing a series of family groups. Using criteria established for this study, 33 of the individuals (9.6%) were "high" excretors of BAIBA. "High" values were approximately 70-200 mg BAIBA/g creatinine. Results were consistent on repeated examinations of urine samples collected at intervals (weeks up to two years). This was considered to be a genetically determined characteristic of the individuals. Although the inheritance pattern could not be determined precisely, the hypothesis that the "character" is determined by a common autosomal gene fit reasonably well with the observed familial distribution.

77. Saenger, E. L.
Metabolic Changes in Humans Following Total Body Irradiation.
DASA-1422 Defense Atomic Support Agency, Washington 25, D. C. (1964).

This report describes results obtained during the period 1 Nov. 1961 - 30 April 1963 from a continuing study of the metabolic effects of total and partial body irradiation. The report represents studies on

29 patients with metastatic or incurable neoplasms who were in good nutritional status and had a stable blood picture. The experimental procedures include an initial sham exposure. Doses of 50 to 200 rad of ^{60}Co γ-radiation were delivered during a single exposure of the whole body. Clinical and laboratory studies are described and summarized in tables and graphs. Results and conclusions from the research include:

1. Development of a new technique for identifying and measuring deoxycytidine (DOC).

2. Identification of DOC in the urine following whole body exposure.

3. Xanthurenic acid was found in the urine of some of the patients after exposure.

4. Chromosomal abnormalities were identified in peripheral blood lymphocytes cultured in the presence of phytohemagglutinin.

5. Patients were found to tolerate doses of 200 rad to the whole body relatively well.

78. Gerber, G., Gerber, G., Kuyohara, S., Altman, K. I. and Hempelmann, L. H.
Urinary Excretion of Several Metabolites in Persons Accidentally Exposed to Ionizing Radiation.
Radiat. Res. 15: 314 (1961).

Urine of three groups of radiation casualties (five Oak Ridge Y-12 casualties, two Los Alamos casualties of the December 1958 criticality accident and two casualties of the Lockport accident of 1960) was analyzed to determine excretion of creatine, creatinine beta-amino-isobutyric acid (BAIBA), pyrrole-carboxylic acid and "free" hydroxyproline at various times after irradiation. In most of the cases, the concentration of BAIBA in urine and the urinary creatine/creatinine ratios were elevated for two weeks after exposure. (The authors do not indicate what their "normal" value represents.) The authors could not demonstrate a relationship between radiation dose (ranging from approximately

There are several sources of uncertainty or error in estimating chromosome aberration frequencies and in using the estimates to evaluate radiation exposures. Following a given radiation dose to the whole body, for example, the aberration frequency may not be the same in all rapidly dividing tissues (60, 62, 63). As mentioned above, aberration frequency decreases fairly rapidly (through cell division) after exposure, and when cells are cultured in vitro to obtain metaphase spreads for chromosome studies, the frequency may also vary with time in culture (62, 63, 64). There are also many variables in the tissue culture techniques used in various laboratories, and these must be taken into consideration when comparing results. Reliable information about the types of radiation and the dose rate are essential (60, 61). The possible influence of agents other than radiation that are known to produce chromosome breaks must also be taken into account (65, 66, 67, 68). In short, numerical data representing the various types of chromosome lesions, like any other type of biological change in any type of disease, are significant only in the context of all other available information about the afflicted individual. Many of the comments about lymphocyte studies in vitro apply to cytogenetic studies on peripheral blood leukocytes.

F. BIOCHEMICAL STUDIES

Changes in the chemical composition of plasma and urine following irradiation have not been conspicuously helpful to the clinician in estimating the degree of injury following irradiation. Neither have the biochemical studies been fruitless, however, and the following radiation-associated changes may warrant further evaluation in this respect.

Urinary excretion of taurine, a sulfur containing amino acid, has been measured in several of the radiation accident casualties. Increased levels were found in some cases, but there is no clear relationship between clinical condition or estimated radiation doses and urinary taurine levels (69, 70, 71). The patterns of taurine excretion after irradiation are species dependent and urinary taurine levels are greatly influenced by dietary protein intake, as is aminoaciduria in general. The concentration of all free amino acids is higher in leukocytes and platelets than in plasma or red cells, an observation that has led Soupart to suggest that the increased urinary excretion of taurine after irradiation may result from release of intracellular taurine secondary to changes in cell permeability (72).

Creatinuria appears promising as a correlate of the radiation dose per gram of muscle. Creatinuria after irradiation of experimental animals (73, 74) and patients receiving radiation therapy (75) represents failure of muscle to utilize newly synthesized creatine which was synthesized at a normal rate (74). Creatinuria in radiation accident casualties has not reflected the severity of the injury particularly well. It will probably be most useful as confirmatory evidence when there is some question about how much of the body may have been shielded. Heavily irradiated patients in the Lockport accident, who were irradiated most intensively over the head and upper thorax, showed very mild creatinuria (creatine/creatinine ratios) compared to the Y-12 casualties who received much more uniform exposure. Thus, one might pair the persistence of relatively normal peripheral blood monocyte levels with relatively low creatine/creatinine ratios in the urine as indications of non-uniform exposure.

Two metabolites of nucleic acid metabolism have been found in increased amounts in the urine of some of the radiation accident casualties and patients receiving whole-body irradiation as therapy. These are beta-aminoisobutyric acid (BAIBA), a product of thymine metabolism, and deoxycytidine (DOC).

The amount of BAIBA normally excreted varies from individual to individual but is generally in the range of 100-200 micromoles per liter of urine except in "high BAIBA excretors" in whom the high excretion of the compound appears to be a hereditary characteristic not associated with overt disease (76). Urinary levels of BAIBA are markedly increased and variable in patients with malignancies (77, 78). Urinary levels of BAIBA were elevated in all five seriously injured Y-12 casualties during the first post-exposure week. Maximum urine concentrations were observed on the fourth post-exposure day and ranged from 250 to 650 μM/L (78). The relationship of urinary BAIBA concentrations to radiation exposure is much less clear in radiation therapy patients, most of whom have malignant disease (77).

After developing an analytic method for measurement of DOC, Saenger and his colleagues measured the concentration of that nucleoside in the urine of two patients before and after they received whole-body therapeutic irradiation. No DOC could be detected in the pre-exposure 24-hour urine specimens (minimum amount detectable was 0.020 mg/hr) but serial 6-hour urine specimens after irradiation showed excretion rates as high as 7.8 mg/hr in one patient and 3.4 mg/hr in the second. Urine of the patient with the highest concentration contained measurable amounts of DOC for two days; that of the other patient only during the first 24 hours after exposure (77).

11. Saenger, E. L., Editor
Medical Aspects of Radiation Accidents, A Handbook for Physicians, Health Physicists and Industrial Hygienists.
U.S. A.E.C. U.S. Government Printing Office (1963).

This handbook was prepared as a guide for medical and health physics personnel in the event of a peacetime radiation accident. It includes sections on estimation of doses, clinical features of the acute radiation syndrome and therapy of of radiation injury.

12. National Committee on Radiation Protection and Measurements Report No. 29, Exposure to Radiation in an Emergency (1962).
Available from Section of Nuclear Medicine, Dept. of Pharmacology, the University of Chicago, Chicago 37, Illinois.

A committee of internationally recognized authorities from the United States, under the chairmanship of Lauriston S. Taylor, reviews the problem of "possible exposures greatly in excess of those encountered in normal radiation work and, in the case of nuclear war, with the certainty that radioactive fallout will kill many of those in the areas involved." Various physical considerations related to estimates of (and control of) exposure are considered. The clinical features of radiation injury are described according to both severity of injury and prognosis. The dividing line between doses that will and will not cause sickness that requires medical care is chosen, arbitrarily, as 200 r. A short section reviews effects on livestock and agriculture and three appendices are included, one on definitions of radiation quantities and units, a second on equivalent residual dose (which is concerned with recovery processes that are active during the period between a first and a subsequent exposure) and a third appendix on empirical relationships between contamination and skin dose.