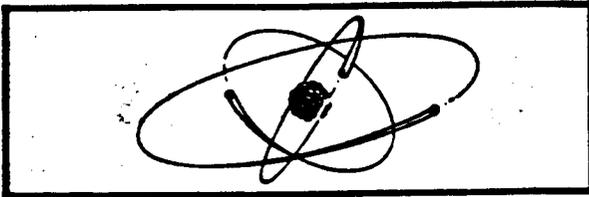


KEREIAKES

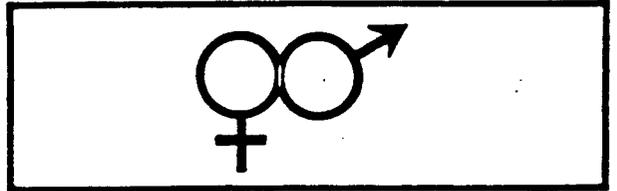
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**JOINT
ORAU-DASA
INFORMATION
EXCHANGE
PROGRAM**

RADIATION EFFECTS



ON



BIOLOGICAL SYSTEMS

*Oak Ridge Associated Universities
Mr W. P. Eck
615-483-8411
7-262*



**OAKRIDGE, TENN.
29-30 March 1971**

JOINT ORAU - DASA INFORMATION EXCHANGE PROGRAM

29 - 30 March 1971

Playhouse Theatre, Jackson Square
Oak Ridge, Tennessee 37830

A G E N D A

Monday, 29 March 1971

- 0800 - 0830 REGISTRATION
- 0830 - 0835 WELCOME - Dr. G. A. Andrews
Oak Ridge Associated Universities
- 0835 - 0840 ADMINISTRATIVE DETAILS
Dr. C. C. Lushbaugh
- Dr. Eugene Saenger, University of Cincinnati - Chairman
- 0845 - 0920 SYMPTOMATIC AND HEMATOLOGICAL EFFECTS OF 300 RADS TOTAL
BODY IRRADIATION
W. Rider
- 0920 - 0945 REPORT OF A RECENT RADIATION ACCIDENT *Lymphs 3000 - 900*
G. A. Andrews and H. Vodopick *WBC 15000 - 25*
- 0945 - 1000 Coffee Break *Platelets 130000 - 25*
creative phosphokina
- Dr. Gould Andrews, ORAU - Chairman
- 1000 - 1020 CLINICAL TOTAL BODY IRRADIATION EFFECTS *1.5 R/hr*
Helen Vodopick and C. Lowell Edwards
- 1020 - 1040 MULTIFACTORIAL ANALYSIS OF HUMAN BLOOD CELL RESPONSES TO
CLINICAL TOTAL BODY IRRADIATION *705 = 12.100.*
J. M. Yuhas, T. R. Stokes and C. C. Lushbaugh *E-6*
- 1040 - 1100 A CLOSED SYSTEM FOR MARROW TRANSPLANTATION
E. B. Silberstein, B. Friedman, S. Toler, and
E. L. Saenger
- 1100 - 1120 HUMAN MARROW CHANGES AFTER TREATMENT WITH LOW-DOSE-RATE
TOTAL - BODY IRRADIATION
F. Goswitz, B. Nelson, H. Vodopick and C. Lushbaugh
- 1120 - 1140 EFFICIENT TESTING IN LARGE ANIMAL EXPERIMENTS
S. G. Levin
- 1140 - 1200 DOSIMETRY FOR TOTAL-BODY IRRADIATION STUDIES
W. L. Beck
- 1200 - 1300 Lunch

Monday, 29 March 1971

- 1620 - 1640 SERUM IMMUNOGLOBULIN (IgG, IgA, IgM), COMPLEMENT (C'3),
AND TRANSFERRIN LEVELS AFTER TOTAL-BODY IRRADIATION
G. Charles Kingdon and Stuart Chaskes
- 1640 - 1700 SERUM AND URINARY AMYLASE ACTIVITIES IN IRRADIATED CANCER
PATIENTS
I. W. Chen, E. B. Silberstein, B. Aron and
E. L. Saenger
- 1700 - 1720 ULTRAVIOLET-ABSORBING COMPOUNDS IN URINE OF TWO IRRADIATED
CANCER PATIENTS AS DETERMINED BY HIGH-RESOLUTION COLUMN
CHROMATOGRAPHY
I. W. Chen, E. B. Silberstein, and E. L. Saenger
- 1720 - 1740 ACETYLCHOLINESTERASE ACTIVITY IN SYNAPTIC VESICLES OF THE
MEDULLA OF RATS EXPOSED TO HIGH DOSES OF GAMMA-NEUTRON
RADIATION
Anthony A. Rene, John H. Darden, and Joe L.
Parker

6:30

7:30 dinner

No host cocktails and dinner at Oak Ridge Country Club.

Tuesday, 30 March 1971

Colonel E. J. Huycke, HQ, DASA - Chairman

- 0900 - 0920 THE PERFORMANCE OF MONKEYS FOLLOWING GAMMA-NEUTRON IRRADIATION AT DOSES FROM 500 TO 16,000 RADS
Donald Barnes, Charles R. Curran, and William F. Davis
- 0920 - 0940 PERFORMANCE DECREMENT AND EEG CHANGES AFTER PULSED IRRADIATION
W. L. McFarland and W. F. Davis
- 0940 - 1000 FISSION NEUTRON RELATIVE EFFECTIVENESS FOR PERFORMANCE DECREMENT IN THE MINIATURE PIG
R. E. George, R. L. Chaput, D. M. Verrelli
- 1000 - 1020 PREVENTION OF EARLY PERFORMANCE DECREMENT/INCAPACITATION FOLLOWING 4000 RADS OF MIXED GAMMA-NEUTRON RADIATION
J. E. Turns
- 1020 - 1040 Coffee Break

Colonel H. B. Mitchell, AFRI - Chairman

- 1040 - 1100 THE RELATIONSHIP OF NAUSEA AND VOMITING TO RADIATION DOSE
E. L. Saenger, E. B. Silberstein, and J. G. Keriakes
- 1100 - 1120 EFFECTS OF RADIATION ON HUMAN ABILITIES
Aaron Wolfgang
- 1120 - 1140 MEASUREMENT OF PERFORMANCE DECREMENT BY IMPEDANCE PNEUMOGRAPHY DURING CONTROLLED EXERCISE AND TOTAL-BODY IRRADIATION IN MAN
Robert C. Ricks, C. C. Lushbaugh and Edward Frome
- 1140 - 1200 AN APPROACH TO ESTIMATING THE COMBINED IMPACT OF HUMAN AND HARDWARE VULNERABILITIES ON SYSTEM PERFORMANCE
Gerald P. Chubb
- 1200 - 1300 Lunch

Dr. John B. Storer, ORNL - Chairman

- 1300 - 1320 TOTAL-BODY IRRADIATION EFFECTS IN SELECTED ANIMAL SPECIES
E. J. Ainsworth

REPORT OF A RECENT RADIATION ACCIDENT

G. A. Andrews and Helen Vodopick
Oak Ridge Associated Universities

On February 4, 1971, a 32-year-old male employee was exposed accidentally to a single large source of ^{60}Co in an Oak Ridge research installation. The major part of the exposure probably occurred in a period of 40 seconds. A thermoluminescent dosimeter worn at waist level gave a reading of 260 Rem; this was believed to be close to the highest dose received except for the hands, which might have received considerably more. On the basis of phantom studies the average bone marrow dose was estimated at about 118 rad.

The patient had characteristic vomiting starting 2½ hours after the accident and continuing intermittently through the afternoon and evening. After that he had no definite symptoms but later reported slight discomfort and numbness in the right hand.

He showed cytogenetic abnormalities compatible with the estimated dose. His hematologic picture has demonstrated sequential changes suggesting a slightly greater degree of injury than anticipated from dose measurements. As of this writing, 29 days after exposure, he had 37,000 platelets and a white count of 3,600 cu mm.

CLINICAL TOTAL BODY IRRADIATION EFFECTS

Helen Vodopick and C. Lowell Edwards
Oak Ridge Associated Universities

Thirteen treatments were given in the low-exposure-rate irradiator during 1970 bringing our total to 37 since the facility was opened in 1967 (C. L. Edwards, G. A. Andrews, Helen Vodopick, Francis A. Goswitz, C. C. Lushbaugh, and R. M. Kniseley). Table tabulates the 1970 exposures by diagnosis, age and sex of patient, exposure, symptoms and response. Only one patient has experienced nausea and vomiting while being treated with LETBI, a 48-year-old woman with chronic granulocytic leukemia (CGL). She consistently has shown good responses to the total-body irradiation medium-exposure-rate irradiation (METBI), LETBI, and fractionated METBI and splenic irradiation, but has experienced gastrointestinal symptoms with each. Other patients occasionally have complained of lethargy or a feeling of weakness and mild anorexia, but no nausea or vomiting.

Experience from previous years indicated that exposures of 250 R in LETBI were probably too much for many patients except polycythemia vera patients with very high platelet counts or those with very high leukocyte counts due to chronic granulocytic leukemia, neither group having received previous suppressive treatment. Consequently, only two patients were treated with 250 R in 1970. Both patients had untreated chronic granulocytic leukemia with total leukocyte counts greater than 100,000/cu mm. Both experienced

MULTIFACTORIAL ANALYSIS OF HUMAN BLOOD CELL
RESPONSES TO CLINICAL TOTAL BODY IRRADIATION

J. M. Yuhas, T. R. Stokes, and C. C. Lushbaugh
Biology Division, Oak Ridge National Laboratory,
and Medical Division
Oak Ridge Associated Universities

Due to the heterogeneity of radiation exposure regimens used in therapy it is often impossible to define a series of exposure groups in the hope of construction dose-response relationships. This difficulty may be overcome by employing a multifactorial analysis which can determine the role of exposure level, dose rate, fraction size and number, and total time, independently of one another. Such an analysis allows the construction of a variety of curves in which response is plotted as a function of one of these variables with the others held constant.

This approach has been applied to the hematologic records of more than 1000 patients subjected to total body radiation therapy for various disorders, with the nadir concentration of white blood cells and/or platelets, for example, used as the measured response. Disease groups include various leukemias and other blood dyscrasias, as well as diseases which do not affect the blood forming tissues directly. The coefficients of multiple correlation have been determined and range from 0.5 to 0.8, indicating that the resultant equations provide an excellent fit of the raw data.

A CLOSED SYSTEM FOR MARROW TRANSPLANTATION

Silberstein, E. B., Friedman, B., Toler, S., and Saenger, E. L.
University of Cincinnati

We have employed marrow auto, iso- and allotransplantation to attempt restoration of normal marrow depressed by irradiation or drugs.

Our technique involves a closed system of marrow storage, filtration and infusion, with no further processing necessary once the marrow is transferred from the aspirating syringe to the storage bag. A double stainless steel filtration system prevents significant fat or bone emboli to the lungs, as indicated by autopsy specimens from a patient dying 3 hours post transplantation of a pre-existing overwhelming necrotizing pneumonitis. The results of marrow transplantation with this technique will be compared to those in the literature.

HUMAN MARROW CHANGES AFTER TREATMENT WITH
LOW-DOSE RATE TOTAL-BODY IRRADIATION

F. Goswitz, B. Nelson, H. Vodopick, and C. Lushbaugh
Oak Ridge Associated Universities

Marrow changes in man after continuous irradiation in the low-dose-rate of 1.5 R/hr have not been reported. Our specially designed irradiation facility directs cobalt-60 teletherapy to the subject from eight corner sources. Since the first patient was treated in July 1967, we have followed the bone marrow changes after 36 treatments in patients with these hematologic disorders: 14 chronic granulocytic leukemia (CGL), 7 polycythemia vera (PRV), 4 primary hemorrhagic thrombocytopenia (PHT), 4 lymphosarcoma (LS), 3 lymphosarcoma-cell postirradiation changes approximately 18 days after the start of treatment in marrow cellularity, fat, GE ratio, erythroid maturation, granulocytic maturation, number of lymphocytes, megakaryocytes, and platelets, and the concentration of iron in histiocytes were compared to the marrows before treatment. Of the 36 treatments, 13 treatments were given with exposures of 100 R, 13 with 150 R, and 10 with exposures of 250 R. The 36 treatments were divided among 26 patients with four treated two times and three thrice.

EFFICIENT TESTING IN LARGE ANIMAL EXPERIMENTS

S. G. Levin
Armed Forces Radiobiology Research
Institute, NIMH, Bethesda
Maryland 20014

Large-Animal experiments are expensive and time consuming. Statisticians have shown that sequential type designs are almost twice as efficient under some conditions. Sequential designs require the outcome of the test on the previous animal in order to determine the test condition of the subsequent animal. If the test sequence permits this, then often savings of almost half the number of animals can be effected; alternately, more precision is "purchases" for the same number of animals committed to an experiment.

Three sequential designs that are appropriate for different conditions will be discussed. The "staircase" and "stochastic approximation" methods obtained when the ED_{50} is required; the Wald sequential test is appropriate when the experimenter wants tests of hypotheses.

DOSIMETRY FOR TOTAL-BODY IRRADIATION STUDIES

W. L. Beck
Oak Ridge Associated Universities

In the Oak Ridge Associated Universities therapeutic total-body (TBI) program three different irradiators are used: the Oak Ridge Associated Universities LETBI and METBI facilities and the UTAEC Variable Dose Rate Irradiation Facility (VDRIF). The facilities provide uniform TBI at exposure rates of 1.5 R/hr (LETBI), 1.5 R/min (METBI) and 40 R/min (VDRIF).

Because of different source-patient geometric and gamma ray energies, the patient's depth dose distribution is not the same in each irradiator. A series of dosimetry experiments using a heterogeneous phantom and thermoluminescent dose measurement technique have been done to determine the complete dose distribution in a patient given TBI in the three irradiators used in our studies. From the data of these studies, we have estimated the average dose to the major organs of the body, e.g., bone marrow, intestines, liver, brain, lenses of eyes, etc.

The importance of using absorbed dose as the basis of comparison is clear from our data; i.e., if two patients were given an exposure of 100 R, one in LETBI and the other in VDRIF, the VDRIF patient would receive a 20% greater marrow dose but his dose to the lenses of the eyes would be 20% smaller than that of the LETBI

CHROMOSOME ABERRATIONS AS A DOSIMETER OF WHOLE BODY IRRADIATION

Silberstein, E. B., Ewing, C., Donovan, J., Kereiakes, J. and Saenger, E. L.
University of Cincinnati

Numerous attempts have been made to employ chromosome aberrations as a radiation dosimeter. Since the appearance of rings and dicentric chromosomes in lymphocytes following irradiation is not difficult to detect, these aberrations have been related to whole body irradiation in doses of 100 or 200 rads for 6 patients where accurate dosimetry is available. Although the patients all had metastatic cancer, there was no evidence of hematologic abnormality other than occasional mild anemia.

Considerable individual variation was found between patients receiving the same irradiation dose and dose-rate. For example, the increment in the total of rings plus dicentrics per cell following 200 rads mid-line absorbed dose ranged from 0.04 to 0.34. Some of the problems inherent in using this system will be discussed.

PAIRED MINIATURE IONIZATION CHAMBERS FOR THE
MEASUREMENT OF NEUTRON AND GAMMA DEPTH
DOSE COMPONENTS IN PULSED REACTOR FIELDS

D. W. Shosa
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

Paired ionization chambers with nominal volumes of 0.05 cm^3 are in use at AFRRRI to measure neutron and gamma components of depth dose distributions in steady-state and pulsed TRIGA fields. The response of the "neutron-sensitive" chamber, which has a wall of tissue-equivalent plastic and is filled with a tissue-equivalent gas mixture, is found to satisfy the requirements of the Fano theorem and has a response equation

$$(1) Q/Q_X = (0.98 \pm 0.03) \bar{\epsilon} N + (1.04 \pm 0.01) \eta \Gamma$$

where Q is the charge (current) measured in the mixed field and Q_X is the charge (current) measured in a $1R \text{ Co}^{60}$ field. $\bar{\epsilon}$ and η are neutron and gamma attenuation corrections and depend on the experimental configuration. N and Γ are respectively the neutron and gamma doses in rads-tissue. A similar response equation for the "neutron-insensitive" chamber with a magnesium wall and CO_2 cavity is

$$(2) Q/Q_X = K \bar{\epsilon} N + (1.04 \pm 0.01) \eta \Gamma$$

where K is estimated to be 0.06 ± 0.02 for free-in-air measurements and 0.04 ± 0.02 for measurements inside a moderator.

COMPARISON OF DOSE PATTERNS IN A MINIATURE
PIG EXPOSED TO NEUTRON AND TO GAMMA RADIATION

D. M. Verrelli, D. W. Shosa
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

The objective of this research effort was to characterize the radiation fields from a nuclear reactor and to compare depth dose patterns for significantly different mixtures of incident radiations.

In an unmodified configuration, the radiation field from the AFRRI-TRIGA reactor is characterized by a neutron-to-gamma ray tissue kerma, free-in-air, of 0.4. An enhanced neutron radiation field was obtained using a cadmium-gadolinium absorber for thermal neutrons coupled with 6 inches of lead shielding to decrease the gamma ray component of the field. A gamma ray field was obtained using 5 inches of water shielding and the same cadmium-gadolinium absorber. Neutron-to-gamma ray ratios, free-in-air, of 10 and 0.06 were obtained for the neutron and gamma ray fields, respectively.

Dose distribution patterns in a miniature pig cadaver were measured for neutron and for gamma radiation fields from the AFRRI-TRIGA reactor. Determination of the radiation components across the brain was performed employing the paired chamber technique. The paired chambers used were 0.05 cm^3 cylindrical-spherical Shonka chambers, one of tissue equivalent plastic filled with tissue equivalent gas and the other of magnesium filled with carbon dioxide gas. Placement of the dosimeters within the cadaver was verified by roentgenology and by dissection of the specimen.

A COMPARISON OF THE GASTROINTESTINAL RESPONSES OF MINIATURE PIGS
TO FISSION NEUTRONS AND TO GAMMA RAYS

S. R. Jones, J. E. West, D. M. Verrelli, and R. E. George
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

To determine the relative effectiveness of fission neutrons in producing lethality from gastrointestinal tract (GI) injury, young adult miniature pigs were bilaterally irradiated in a neutron field or a gamma ray field (incident neutron/gamma ratios of 5 and 0.06, respectively) obtained with the AFRRI-TRIGA reactor. Midline tissue doses from the neutron and gamma ray fields ranged from 360 to 1970 rads and 605 to 2630 rads, respectively. All doses were delivered at 250 rads/min and the depth dose measurements indicated the irradiations were uniform (class A) to the intestinal tract. Biological end points measured included lethality, survival time, gross and microscopic pathology, weight loss, and proliferation of bacterial flora in selected tissues at necropsy. Using a 7.5 day survival time as the lethality end point, the LD₅₀ for GI death was calculated by probit analysis as 430 rads for the neutron field and 870 rads for the gamma ray field (a relative effectiveness of 2.0 for the neutron field). Using least squares fitted regression lines, midline tissue doses corresponding to 7.5 day survival time were found to be 430 rads for the neutron field and 920 rads for the gamma ray field (a relative effectiveness of 2.1 for the neutron field). The relative segmental GI radiosensitivity of both neutron- and gamma-irradiated pigs

ACTIVE BONE MARROW DOSES IN WHOLE BODY AND PARTIAL BODY EXPOSURES

J. G. Kereiakes, E. B. Silberstein, E. L. Saenger, W. Van de Riet, and C. Born,
University of Cincinnati

The University of Cincinnati College of Medicine has a program for whole body exposure and for partial body exposure (either upper body, lower body, or complete trunk) of patients for the treatment of cancer. The radiation is delivered bilaterally by a Cobalt-60 teletherapy unit. The air exposure at the location of the patient's midline to provide a desired midline absorbed dose in rads is specified.

The full quantitative characterization of dose and dose effect relationships are necessarily more complex for non-uniform than for uniform doses. With non-uniform exposures, it has been difficult to normalize a dose parameter (as midline air exposure, midline absorbed dose, exit dose, integral dose or average dose) with observed effects. This study attempts to investigate "active bone marrow dose" as a parameter for whole body and partial body exposures. Thermoluminescence dosimetry (lithium fluoride) was used to determine total active bone marrow doses in a tissue-equivalent human phantom (Alderson Rando) exposed under similar conditions as patients. (For the various phantom exposure conditions, total active bone marrow doses, and dose equivalents (using relationships between animal and stem cell dose-survival curves) were determined.

Exposure condition	Active bone marrow-dose g. rads per R midline air exposure	Dose equivalent per R midline air exposure
Whole body	913	0.674 rad
Upper body	436	0.276 rad
Lower body	558	0.354 rad
Complete trunk	685	0.451 rad

OXIDATIVE SWELLING AND PHOSPHORYLATION IN RAT LIVER MITOCHONDRIA:
COMBINED EFFECTS OF LINOLEATE, STARVATION, GLUCOSE, AND X IRRADIATION

Skidmore, W. D. and Catras, G. N.
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Institute, NNMC, Bethesda
Maryland 20014

The objective of this study was to determine the effects of whole-body x irradiation on structural and functional integrity of rat liver mitochondria. The investigation was designed to approach the objective by intercomparing effects of (a) ethyl linoleate in the diet, (b) starvation, (c) intraperitoneal glucose, and (d) whole-body x irradiation on oxidative swelling and oxidative phosphorylation. Iron-induced mitochondrial swelling associated with lipid oxidation was used as an index of injury to the structural integrity of the outer membranes. Oxidative phosphorylation with succinate as substrate was selected as an index of the functional integrity of the inner membranes. In rats exposed to 1000 R, the lag time for oxidative swelling was found to be decreased below that for controls 24 hours postexposure and the efficiency of oxidative phosphorylation was increased above the controls. Although direct effects on molecular structure cannot be ruled out, the data of the present study strongly implicate an indirect effect of radiation-induced starvation, particularly as indicated by the assay for oxidative swelling. The results support the conclusion that whole-body x irradiation induces a structural

ALPHA-AND BETA ADRENERGIC ACTIVITY OF THE DOG
CARDIOVASCULAR SYSTEM DURING THE DEVELOPMENT
OF THE G.I. RADIATION SYNDROME

J. Kabal and S. J. Baum
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

The objective of this study was to measure the alpha-and beta-adrenergic activity of the dog cardiovascular system during the development of the G.I. radiation syndrome. Dogs were exposed to 1500 rads (midline tissue dose) of mixed gamma-neutron radiation. Hemodynamic parameters of an in situ intestinal loop were measured in response to systemic administration of norepinephrine and isoproterenol and to gradual bleeding-reinfusion. Autoregulatory disturbances were manifested beyond 48 hours postirradiation. At 48 hours postirradiation, a neuro-humoral-imbalance was detected. Later at 72 hours, the inherent vaso-compensation to sudden blood pressure changes deteriorated markedly. In addition, cardiac hemodynamic parameters were measured after epinephrine administration. At 72 hours postirradiation significant changes in cardiac output and peripheral resistance were observed. There were no indications for radiation induced adrenergic receptor blocking activity.

THE EFFECT OF 6 MEV X-RAY IN SUPRALETHAL DOSES
ON THE MAINTENANCE OF SERUM GLUCOSE LEVELS

Capt Fred N. Beckman, Maj Dan J. Craig,
Dr. Marc A. Nathan, Maj Earl L. Kinsley
School of Aerospace Medicine

Serum glucose changes as a function of 6 Mev x-rays delivered at approximately 170 r/min. were measured in six chloralose anethetized rhesus monkeys. The total dose was 10 Krad delivered in 1 Krad increments. Two pre-irradiation serum samples were drawn to establish fasting blood glucose levels. Following each 1 Krad increment a succeeding blood aliquot was taken. In addition, two unanesthetized animals were similarly exposed and blood samples taken.

Glucose levels in chloralose anethetized animals were noted to be significantly lower than previously reported normal fasting glucose. Serum glucose in these irradiated animals remained constant or increased slightly until 7 Krad when a significant hypoglycemia as compared to controls was noted. Awake unanesthetized preparations, however, demonstrated a moderate to marked hyperglycemia in the 3-7 Krad range.

Chloralose anesthesia appears to block the rise in serum glucose seen in the unanesthetized preparations. It has been shown that chloralose blocks hormonal function of the adrenal medulla. Hyperglycemia in experimental animals exposed to ionizing radiation has been attributed to a conversion of amino acids to glucose with a following rapid clearance of reducing substances. It may be that the rate of rise or fall of the level of serum glucose in whole body irradiated animals depends upon the rate of conversion of amino acids to glucose and upon glycogenolysis--an epinephrine dependent reaction.

PROGNOSTIC SIGNIFICANCE OF CONCENTRATIONS OF FOUR CLASSES OF
PROTEIN-BOUND CARBOHYDRATES IN THE SERUM OF DOGS

Adelbert S. Evans
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

To establish criteria for assessment of continuing prognosis of an individual, tests should be selected which measure changes directly proportionate with the gravity of his condition. To make the testing procedure objective, numerical boundaries should be established so that crossing from one range to another is indicative of changes in the probable course of the patient.

Four classes of protein-bound carbohydrates were examined in the serum of dogs at intervals after irradiation, and their changes were related to observed clinical condition of the animals and their ultimate fate (survived or died). Moderate to marked fluctuations were seen during the testing period in the protein concentration (mg CHO/100 mg protein) of neutral hexoses, sialic acid, and hexosamines. The protein concentration of neutral hexoses gave the clearest warning of unfavorable prognosis in the animals which died and exhibited the greatest stability in those which survived. No significant changes in the concentration of protein-bound fucose were seen in any of the dogs.

Numerical ranges of protein concentrations of neutral hexoses are proposed to indicate good, guarded, and poor prognosis for this species. These tentative ranges were tested in 15 additional dogs and found to be effective for prediction.

SERUM IMMUNOGLOBULIN (IgG, IgA, IgM), COMPLEMENT (C'3)
AND TRANSFERRIN LEVELS AFTER TOTAL-BODY IRRADIATION

G. Charles Kingdon and Stuart Chaskes
Oak Ridge Associated Universities

The effect of total-body gamma irradiation (TBI) on serum immunoglobulin, complement (C'3) and transferrin levels was studied in 29 patients. Total exposure ranged from 100 R to 500 R given as a fractionated dose of 30 R/day at a dose rate of 1.5 R/hr or 1.5 R/min, or as a single exposure of 500 R delivered at a dose rate of 45 R/min. Immunoglobulin depression began between 4 days and 21 days after an exposure of 100 R to 250 R; C'3 and transferrin levels also decreased. A 20% or greater reduction in IgG, IgA, or IgM levels occurred in 46%, 57% and 43% of the patients respectively. Decreases of 40% or more in IgG, IgA or IgM were seen in 3.5%, 21.5%, and 18% of the patients. Partial and often complete recovery of IgG, C'3 and transferrin levels was observed by 6 weeks; IgA and IgM levels often remained depressed longer. Immunoglobulin levels of the patient exposed to 500 R began a progressive fall 14 days after irradiation and reached a level of less than 20% of pre-treatment values by 121 days. Total serum proteins also decreased approximately 50%, however, this was not sufficient to account for the large immunoglobulin decreases. Three patients having severely depressed immunoglobulin levels died with bacteremia. These data suggest that altered immunoglobulin levels may in part explain the increased infection rates in patients exposed to TBI.

SERUM AND URINARY AMYLASE ACTIVITIES
IN IRRADIATED CANCER PATIENTS

I. W. Chen, E. B. Silberstein, B. Aron, and E. L. Saenger
University of Cincinnati

Amylase activities in serum and urine of patients in the various cancers were studied before and after they received whole body and partial body ⁶⁰Co-irradiation. Significant increases in serum amylase activity were observed in 8 out of 11 patients 20 to 24 hours after whole body irradiation. The average increase for 5 patients receiving 200 ^{rads} R was 13.9-fold, whereas that for 4 patients receiving 100 ^{rads} R was 4.8-fold. The serum amylase was not elevated significantly in all of patients receiving radiation to their lower bodies (excluding head) with the exception of one patient who gave a 3.2-fold increase after receiving 300 ^{rads} R. One patient with 300 ^{rads} R to her upper body (including head) showed a 20-fold increase in the serum amylase activity. Increases in urinary amylase activity ranging from 10.1 to 2.4-fold were observed in all patients receiving whole body irradiation. Preliminary studies with agar electrophoresis indicate that the serum amylase produced after irradiation originated from salivary glands. Irradiation of dogs and rats did not result in increased amylase activity in urine or serum.

ULTRAVIOLET-ABSORBING COMPOUNDS IN URINE OF TWO IRRADIATED
CANCER PATIENTS AS DETERMINED BY HIGH-RESOLUTION COLUMN
CHROMATOGRAPHY

I. W. Chen, E. B. Silberstein, and E. L. Saenger
University of Cincinnati

Urinary excretion of ultraviolet-absorbing compounds by two cancer patients before and after radiation therapy was studied by the use of high resolution anion exchange column chromatography. The first patient studied was a 14 year old male with Ewing's Sarcoma treated with 100 ^{rads} ~~Rads~~ to the whole body. Chromatograms of his pre- and post-irradiation urine samples showed no significant change with the exception of the peak corresponding to hypoxanthine. Daily excretion of hypoxanthine was 0.02 mg per Kg body weight before irradiation and 0.06 mg/Kg after irradiation. The second patient was a 58 year old female with carcinoma of colon, who received 300 ^{rads} ~~Rads~~ to her lower body. Daily excretion of hypoxanthine also increased from 0.04 to 0.23 mg/Kg. In addition, Xanthine increased from 0.03 to 0.11 mg/Kg, pseudo-uridine from 0.70 to 1.90 mg/Kg, and uracil from 0.006 to 0.18 mg/Kg. Five other unidentified ultraviolet-absorbing compounds in post-irradiation urine were elevated at least 10-fold as compared to those in pre-irradiation urine. (Supported by Contract DASA-01-69-C-0131 of the Defense Atomic Support Agency.)

ACETYLCHOLINESTERASE ACTIVITY IN SYNAPTIC VESICLES OF THE MEDULLA
OF RATS EXPOSED TO HIGH DOSES OF GAMMA-NEUTRON RADIATION

René, Anthony A., Darden, John H., and Parker, Joe L.
Armed Forces Radiobiology Research
Institute, NNMC, Bethesda
Maryland 20014

Sprague-Dawley rats were subjected to a whole-body dose of 15 Krads of mixed gamma-neutron radiation. At 2 and 24 hours following irradiation 14 animals from the irradiated group and 14 unirradiated controls were sacrificed by replacing the blood in the brain circulation with a perfusion of a sucrose- eserine solution. The medulla section of the brain was removed, homogenized and prepared for ultracentrifugation and sucrose density gradient separation. The separated synaptic vesicles were assayed for protein and acetylcholinesterase (ACHE). A decrease in protein was found 2 hours after irradiation with a greater decrease 22 hours later. A decrease in ACHE activity was also seen 2 hours after irradiation but there was no further decrease at 24 hours. These results will be correlated with vascular changes found in animals undergoing the Central Nervous System (CNS) syndrome.

THE PERFORMANCE OF MONKEYS FOLLOWING GAMMA-NEUTRON
IRRADIATION AT DOSES FROM 500 TO 16,000 RADS

Donald Barnes, Charles R. Curran, William F. Davis
Armed Forces Radiobiology Research
Institute

The ability of monkeys to perform learned tasks following exposure to a single pulse of mixed spectrum radiation will be reviewed. The data to be presented includes studies from the School of Aerospace Medicine with doses from 500 to 5000 rads and from the Armed Forces Radiobiology Research Institute with doses from 2000 to 16,000 rads. The variations in performance observed at the two laboratories and possible causative factors resulting from differences in radiation source, exposure geometry or experimental procedure will be discussed.

PERFORMANCE DECREMENT AND EEG CHANGES
AFTER PULSED IRRADIATION

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Six adult male rhesus monkeys were used to investigate the relationships between behavior and EEG after a pulsed 2500 rad dose of mixed gamma-neutron radiation. Monkeys were implanted with stainless steel recording electrodes on the dura and then trained on a visually cued shock avoidance task requiring both response and inhibition of response to appropriate stimuli. EEG data on magnetic tape was later digitized and a power spectral density analysis of selected 10 second epochs carried out on a computer. After the monkey reached a stable level of performance, he was exposed to a 2500 rad pulse. Behavior and EEG were monitored for an hour after the pulse and periodically until death. Maximum incapacitation in the positive response category appears 5-15 minutes after pulse, whereas maximum disturbance in inhibition of response appears 15-30 minutes after pulse. A shift in EEG spectrum from the normal low voltage fast activity to a high voltage slow wave pattern closely followed the onset of behavioral incapacitation. There was a reversion of the EEG pattern to a normal frequency spectrum concomitant with behavioral recovery. The results indicate that the EEG can be used as an index of radiation induced behavioral impairment.

FISSION NEUTRON RELATIVE EFFECTIVENESS FOR PERFORMANCE DECREMENT IN
THE MINIATURE PIG

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Miniature pigs, trained to cross a shuttlebox on cue, were supralethally irradiated in a nuclear reactor-produced neutron field; their postirradiation performance was compared to that of pigs similarly irradiated in either a gamma ray field or a mixed gamma-neutron field produced with the same reactor. The neutron field consisted of approximately 90 percent neutrons and 10 percent gamma rays; the gamma field was about 5 percent neutrons and 95 percent gamma rays; the mixed field was about 30 percent neutrons and 70 percent gamma rays. Since it had been shown that radiation damage to head structures was the cause of early permanent incapacitation, early transient incapacitation (ETI), and early death in these pigs, dose to the middle of the brain was used as the reference for comparisons. The dose rate at that point was approximately 2000 rads/min for all irradiations and doses ranged from 1500 to over 36,000 rads. Distribution of dose across the brain and ratio of midbrain to mid trunk doses did not vary greatly among the neutron, gamma and mixed field irradiations.

The miniature pig's response to the fission neutron field was quite different from its response to similar doses from the gamma ray field. Early performance decrement, including ETI and early permanent incapacitation, occurred following much lower doses from the gamma

PREVENTION OF EARLY PERFORMANCE DECREMENT/INCAPACITATION FOLLOWING
4000 RADS OF MIXED GAMMA-NEUTRON RADIATION

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Monkeys (M. mulatta) were trained to perform a discrete-trial, cued avoidance task. Femoral catheters were then placed, under sodium pentobarbital anesthesia, to record blood pressure values, and the animals were irradiated 3 days postoperatively. Each animal received 4000 rads of mixed gamma-neutron radiation delivered as a single pulse.

Ten animals were treated with norepinephrine infusion following irradiation. There was no consistent correlation between blood pressure and postirradiation performance. Some performed poorly even though blood pressure was maintained at normal or near normal levels: one animal, however, performed satisfactorily for some time even though his mean arterial blood pressure could not be maintained above 40 mm Hg.

Another series of studies has been started using an antihistamine as pretreatment. To date, six trained animals have been irradiated, and only one has failed to perform satisfactorily during the first 30 minutes postexposure. The untreated control monkeys consistently suffer performance decrement within 30 minutes following 4000 rads of pulsed mixed gamma-neutron radiation.

THE RELATIONSHIP OF NAUSEA AND VOMITING
TO RADIATION DOSE

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Patients with metastatic carcinoma were irradiated with ^{60}Co gamma rays in doses up to 250 rads to the whole body, 300 rads to upper body (above the xiphoid process) or lower body (below the xiphoid process) or 200 rads from manubrium to pubis. The dose rate was 4 to 5 rads per minute. These patients were clinically stable without anorexia, nausea or vomiting prior to treatment.

The incidence of nausea and vomiting, duration, and latent period were noted for these groups. The latent period for nausea and vomiting was quite short, rarely exceeding three hours. The incidence of nausea and vomiting rose from nil at 60-70 rads to 67% at 200 rads whole body irradiation. Symptoms were less likely to occur with upper than with lower body irradiation at the same doses.

EFFECTS OF RADIATION ON HUMAN ABILITIES

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A 14 minute color film describes an ongoing project designed to assess to what degree and on what types of tasks human abilities would be affected when exposed to varying amounts of ionizing irradiation to the brain or spinal cord. Only subjects who have no damage to the central nervous system are included in the study. The film shows a subject undergoing radiation treatment for a tumor of the scalp and how radiation penetrates through the scalp with different amounts of radiation being absorbed at varying depths of the brain. The subject is shown performing on an objective battery of tests that are administered before treatment, middle of treatment, end of treatment, and 1, 3, and 6 months following treatment. The tests are described and include measures of motor coordination, muscle strength, anxiety, motivation, memory and tasks involving speed and accuracy in decision-making. The subject, when interviewed, describes some difficulties he had in remembering but these difficulties were temporary. The practical implications of the research are discussed and data concerning people's reactions toward individuals accidentally exposed to radiation is presented.

MEASUREMENT OF PERFORMANCE DECREMENT BY IMPEDANCE
PNEUMOGRAPHY DURING CONTROLLED EXERCISE
AND TOTAL-BODY IRRADIATION IN MAN

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Since the inception of man's space efforts many exhaustive tests have been performed to determine physiologic responses to hostile environments. Early experiments included the physiological effects of centrifugation (G-force studies), weightlessness, and short-or long-term confinement (capsule simulation). Recent space missions, which transversed the Van Allen radiation belts and were extended in time, have increased the necessity for a more thorough understanding of man's performance ability in the event of exposure to ionizing radiations. The need for this experimentation is particularly enhanced by the fact that orbiting space stations (now in planning stages) will be powered by on-board nuclear reactors that will expose crew members to low, well-defined total-body irradiations. Less predictable galactic and solar radiations add to the possibility of incapacitation by radiation exposures. However, few experimental situations arise in which man is routinely exposed to total-body irradiations. In order to investigate the performance decrement effects of total-body irradiation we measured respiratory function (via impedance pneumograph) in patients with chronic leukemia exposed to therapeutic levels of ^{60}Co gamma radiation. Selected patients exercised

AN APPROACH TO ESTIMATING THE COMBINED IMPACT OF HUMAN
AND HARDWARE VULNERABILITIES ON SYSTEM PERFORMANCE

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Most weapons systems involve both man and machine. Hardware studies of nuclear survivability/vulnerability (S/V) have, until recently, treated crew vulnerabilities separately. First attempts to treat crew vulnerabilities on a more explicit basis similarly assumed the hardware degradation had no impact on an assessment of human vulnerability.

During the last six months, the Aerospace Medical Research Laboratory has been developing an approach for combining both hardware and human vulnerability assessments into an integrated evaluation of system vulnerability/survivability. A method has been devised for describing hardware degradation, and the logic has been developed for inferring how these operating deficiencies may affect the sequence or difficulty of tasks following exposure to a nuclear event. The Monte Carlo simulation model that was revised to reflect the impact radiation induced performance decrement might have on mission success is now being further modified to include these new considerations as well.

Data are now being collected to determine how pilots respond

TOTAL-BODY IRRADIATION EFFECTS IN
SELECTED ANIMAL SPECIES

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The presentation draws from published work, unpublished but completed studies and work in progress, to evaluate critically generalizations regarding responses of various species to total-body photon and neutron irradiations. Salient features of single and split-dose lethality studies with rodents, swine, sheep and dogs exposed to 1 Mvp X-rays are summarized. In addition to differences in recovery "rates", some species exhibit delays in onset of recovery and a phase of increased radiosensitivity which succeeds a period of rapid recovery. Responses of swine and sheep to protracted ⁶⁰Co gamma irradiation illustrate a relationship between recovery ability, measured by split-dose LD₅₀ determinations, and recovery potential during protracted irradiation. One experiment with sheep explored additivity of an acute sublethal exposure followed by protracted exposures at 4R/hr. Complete additivity was observed under these circumstances, as predicted from earlier split-dose lethality studies which showed an extended no-recovery period after acute exposure. A summary of lethality studies in dogs includes dose-survival time relationships after supralethal exposure to pulsed gamma/neutron radiation, and LD_{50/30} estimates for fission spectrum neutrons, 14.7 Mev neutrons and 1 Mvp X-rays. The High Level Exposure Room adjacent to Argonne's JANUS reactor provides an excellent facility for study of fission neutron effects on

RADIATION EXPOSURE RATE DEPENDENCY OF THE IMMUNE RESPONSE

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The depressive effect of ionizing radiation on the immune mechanism has been documented in a variety of species under a variety of experimental conditions. Although several dependent and independent variables must be considered in attempting to evaluate the effect of radiation on the immune response, four may be considered to be of primary importance: (1) radiation dose; (2) radiation quality; (3) radiation exposure rate; and (4) the temporal relation of antigen injection and radiation exposure. Studies in our laboratory have recently emphasized a reevaluation of point (3). In radiation immunology, exposure rate studies have generally fallen into three broad categories; (A) acute, i.e. radiation given in a matter of a few minutes or hours; (B) chronic, i.e. radiation administered continuously over days, weeks, or months; and (C) fractionated, i.e. acute or chronic radiation given in increments at fractional (hourly, daily, etc.) intervals until a desired total dose is obtained. Relative to category (A) it has tacitly been assumed that radiation delivered in a few hours is comparable in its immunosuppressive effects to radiation delivered in a few minutes. Our studies, however, show that this relatively small differential in radiation time has a marked effect on the degree of immunosuppression achieved. Thus, within this so-called "acute" exposure period, it has been found that radiation given in a few minutes is far more suppressive than the same radiation dose given in a few hours. Extrapolation of this information to a potential clinical situation, the engraftment of foreign marrow, has revealed

ANALYSIS OF SURVIVAL AND CAUSE OF DEATH STATISTICS FOR MICE
UNDER DURATION-OF-LIFE GAMMA IRRADIATION

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The late effects of protracted lifetime exposure to low levels of external radiation continue to be a matter of operational concern. Studies have been carried out on several inbred mouse strains and hybrids irradiated from young adulthood to different daily exposure levels of ^{60}Co gamma irradiation. The levels include 0.3, 1.3, 2.6, 6, 12, 24, 32 R/day and above. The lowest level is roughly comparable to the occupational MPD for the atomic energy industry.

At the lowest dose, there is little evidence of life-shortening, but as exposure increases, there is an exponential decline in life expectancy with increasing daily dose. The life-shortening coefficient is approximately 4 days/100R accumulated or 4%/R/day.

The experiment revealed that when life-shortening is ≤ 15 percent, all of the increased mortality can be attributed to radiation-induced increases in the death rates from neoplastic diseases, including various forms of leukemia, pulmonary tumors, and tumors of the female reproductive system. The age-specific death rates for mice dying of all other causes remain the same as the controls throughout life, at the lowest dose levels. At 6 R/day, a non-neoplastic disease component of excess mortality rate begins to emerge. This increases rapidly with increasing daily exposure level.

INFLUENCE OF HYPOTHERMIA-HYPERCAPNIA ON TERATOLOGIC EFFECTS
OF WHOLE-BODY GAMMA IRRADIATION IN FETAL RAT BRAIN

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Timed-pregnancy albino rats were exposed, on gestation day 13.5, to single doses of whole-body gamma (Co^{60}) irradiation from 25 R to 200 R (50 R/min.) in increments of 25 R. Animals of another group received an initial exposure of 100 R followed in 9 hours by second doses of 50 R or 100 R. A third group was exposed to the same irradiation regimens as the second group, but hypothermia-hypercapnia (R.T. 20° C to 75 minutes) was induced in these rats immediately after the initial irradiation exposure. A fourth group was exposed to a single dose of 100 R followed immediately by hypothermia-hypercapnia but without further radiation exposure. On gestation day 19.5 the cross sectional area of primordial cerebral cortex was determined at the rostro-caudal mid-point of the cerebral hemisphere, and mean values for all groups were plotted on a semi-log scale. The resulting graph revealed a dose-response curve with a shoulder zone between 25 R and 75 R in the single dose group. In the split-dose groups mean values were higher than in animals exposed to comparable doses in single exposures. In animals subject to hypothermia-hypercapnia in the interval between the two exposures and following only a 100 R

IN VITRO STUDIES OF CHROMOSOME ABERRATIONS
CAUSED BY IRRADIATION

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There is considerable inter-laboratory variation in the dose-response relationship between in vitro lymphocyte irradiation and the production of dicentric and ring chromosome aberrations. In an attempt to clarify the role of some of the many variables in this in vitro system, lymphocytes were irradiated under varying culture conditions and at three dose rates to a total of 300 rads. Preliminary results to date suggest definite variations in the test system response depending on whether the dose rate is 4, 75, or 300 rads per minute and whether the lymphocytes are irradiated in whole blood or in culture. (Supported by Contract DASA-01-69-C-0131 of the Defense Atomic Support Agency.)