U

SECURITY

AD-A199 392

DTIC FILE COPY

(1)

NTATION PAGE

Form Approved
OMB No. 0704-0188

ELECTE SEP 27 1988 S D H

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT: Approved for public release; distribution is unlimited.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): USAFSAM-PROC-87-16	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: USAF School of Aerospace Medicine	6b. OFFICE SYMBOL (If applicable): USAFSAM/RZP
6c. ADDRESS (City, State, and ZIP Code): Human Systems Division (AFSC) Brooks AFB, TX 78235-5301	7a. NAME OF MONITORING ORGANIZATION
8a. NAME OF FUNDING / SPONSORING ORGANIZATION: USAF School of Aerospace Medicine	8b. OFFICE SYMBOL (If applicable): USAFSAM/RZP
8c. ADDRESS (City, State, and ZIP Code): Human Systems Division (AFSC) Brooks AFB, TX 78235-5301	7b. ADDRESS (City, State, and ZIP Code)
	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER

10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO	PROJECT NO.	TASK NO	WORK UNIT ACCESSION NO
62202F	7757	04	48

11. TITLE (Include Security Classification)
A 20 Year Review of Mortality in Proton Irradiated Monkeys

12. PERSONAL AUTHOR(S)
Yochmowitz MG; Wood DH; Salmon YL; Hardy KA

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Interim Report	FROM 1964 TO 1987	1987	2

16. SUPPLEMENTARY NOTATION
An article appearing in Transactions of the American Nuclear Society, 55: 540-541(1987).

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Protons; Cosmic Radiation; Mortality; Radiation Effects
06	01		
06	18		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A group of 51 control and 217 proton irradiated monkeys has been under observation since 1964. This report summarizes by dose, energy, and sex the latent effects of radiation observed in this group. Irradiated animals had significantly higher mortality than controls, 62% versus 43%. In pooled data, doses and energies which shortened life were ≥ 360-400 rad and ≥ 55-MeV. Lower proton energies and doses were more effective in females (32-MeV and 25-113 rad, respectively) than in males (55-MeV and 360-400 rad, respectively).

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Michael G. Yochmowitz	(512)536-3882	USAFSAM/RZM

DD Form 1473, JUN 86 — Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

maneuvers have minimal impact on operations. Safe landings can be made at fallout-free fields with only simply emplaced radiation detectors that can be interrogated. Routine operation of a similar system is now utilized for snow depth monitoring in remote areas.

CONCLUSIONS

The evaluation of analytical procedures, test experiences, assessment of lessons learned, improvements in radiation detectors, and training/simulation exercises over the past four decades has led to the development of adequate procedures and tools for radiation protection during military operations. A recent air defense exercise centered at McCord AFB properly utilized all the available tools. There was a long period of careful planning by an aggressive staff. They consulted many technical experts on weapons effects, expedient shelters, and decontamination procedures. They obtained and used the National Shelter Survey data tapes for building availability in dispersed locations. They coordinated and made joint plans with all agencies in the Northwest Regional Emergency Planning Council and carefully examined every aspect of the air defense operations. The result was a very successful dispersed air defense operation in the face of a simulated massive attack (blast destruction of all major facilities and heavy fallout in most areas). Both air crews and ground crews were able to survive the simulated environments (as judged by monitors) and work effectively.

2. A 20-Year Review of Mortality in Proton-Irradiated Monkeys, *Michael G. Yochmowitz, David H. Wood, Yolanda L. Salmon, Kenneth A. Hardy (USAFSAM), invited*

INTRODUCTION

The U.S. Air Force School of Aerospace Medicine (USAFSAM) and the National Aeronautics and Space Administration (NASA) initiated a series of experiments in 1964–65 to study the acute effects of protons in rhesus monkeys.[a] The rationale for the selected doses and energies are given by Dalrymple and Lindsay.[1] In brief, five exposure energies—32, 55, 138, 400, and 2300 MeV—were selected to represent the proton spectrum in space. The 32-MeV energy approximated a 1-cm depth penetration to determine effects on skin and subcutaneous tissue. The 55-MeV energy yielded a 2.5-cm depth of penetration and reached radiosensitive bone marrow and the gastrointestinal tract. The higher energies, 138, 400, and 2300 MeV, provided uniform depth dose distributions throughout the animals. The 400-MeV energy approximates the highest energy particle found in significant concentrations in the Van Allen belts, and the 2300-MeV particle simulated very high-energy galactic cosmic particles. Doses varied between 25 and 800 rads and dose rates varied from 12.5 to 100 rad/min. The acute studies yielded LD 50/30 estimates and have been published.[2–6]

Those subjects surviving the initial 90-day postexposure period along with controls and subjects of similar age exposed to X rays, electrons, and protons of mixed energies have become part of a lifetime study of delayed radiation effects. Those subjects and their nonirradiated controls are referred to as the "Chronic Radiation Colony." The initial proton subjects entering the colony consisted of 31 control (20 males, 11 females) and 217 survivors (124 males, 93 females).

[a]The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act, and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, National Research Council.

Reports in the open literature include a case of granulocytic leukemia at 3 yr (Ref. 7), 4- and 5-yr reports on tumors and cutaneous and subcutaneous effects,[8,9] a 6-yr finding of weight loss,[10] a 6- to 7-yr diagnosis of endometriosis,[11,12] a 9-yr summary of mortality experience,[13] a 15-yr summary of endometriosis findings,[14] a 17-yr summary of mortality experience,[15] and the occurrence of brain tumors.[16]

DESCRIPTION

Detailed descriptions of the dosimetry and exposure have been published.[17,18] Dose groupings used are 0, 25 to 113, 200 to 280, 360 to 400, 500 to 650, and 800 rads. These dose groupings began at the lowest exposure, 25 rads, and formed 100-rad intervals with the available doses. The 25 to 125 interval became 25 to 113 rads, since 113 was the highest dose in that range. The exception was 500 to 650 rads, which included three 650-rad subjects.

This report summarizes by dose, energy, and sex the latent effects observed in the Chronic Radiation Colony to date.

RESULTS

The pooled data provided the following information:

1. Irradiated animals had significantly higher mortality than controls: 62% versus 45%.

2. The 55-MeV mortality (61%) was similar to the totally penetrating 400- (60%) and 2300-MeV (57%) exposures.

3. Doses and energies that shortened life were ≥360 to 400 rads and ≥55 MeV.

4. Death rates compared to controls began to increase after ~8 yr in 400 rads, after ~2 yr in 500 to 600 rads, and ~1 yr in the 800-rad subjects.

5. Of nine probable causes of death, the leading causes were primary infections (28%), endometriosis (21%), organ degeneration (19%), and malignant neoplasms (20%).

Data comparing males and females provided the following information:

1. Mortalities in irradiated males (51%) and females (76%) were significantly higher than in respective controls (35% and 55%).

2. Lower proton energies and doses were more effective in females (32 MeV and 25 to 113 rads, respectively) than in males (55 MeV and 360 to 400 rads, respectively).

3. Deaths occurred earlier in females than in males from exposures as low as 25 to 113 rads and at all exposure energies studied except 55 MeV.

4. The development of endometriosis in females and neoplasms in males is enhanced significantly by proton irradiation over that of respective controls.

5. The development of endometriosis at relatively low-exposure energies (e.g., 32 MeV) and doses (e.g., 25 to 113 rads) of protons may be a limiting factor for female astronauts in extended missions in space where particle radiations are prevalent.

1. G. V. DALRYMPLE, I. R. LINDSAY, "Protons and Space Travel—An Introduction," *Radiat. Res.*, **28**, 365 (1966).

2. G. V. DALRYMPLE, I. R. LINDSAY, J. J. GHIDONI, H. L. KUNDEL, E. T. STILL, R. JACOBS, I. L. MORGAN, "Some Effects of Whole-Body 32-MeV Proton Irradiations on Primates," *Radiat. Res.*, **28**, 406 (1966).

3. I. R. LINDSAY, G. V. DALRYMPLE, J. J. GHIDONI, J. C. MITCHELL, I. L. MORGAN, "Some Effects of 55-MeV Protons on Primates," *Radiat. Res.*, **28**, 446 (1966).

4. G. V. DALRYMPLE, I. R. LINDSAY, J. J. GHIDONI, J. D. HALL, J. C. MITCHELL, H. I. KUNDEL, I. L. MORGAN, "Some Effects of 138-MeV Protons on Primates," *Radiat. Res.*, **28**, 471 (1966).

5. G. V. DALRYMPLE, I. R. LINDSAY, J. J. GHIDONI, J. C. MITCHELL, I. L. MORGAN, "Some Effects of 400-MeV Protons on Primates," *Radiat. Res.*, **28**, 507 (1966).

6. I. L. LINDSAY, G. V. DALRYMPLE, "Acute Somatic Effects in Primates of Protons to 400-MeV," *Radiat. Res.*, 7 (Suppl.), 330 (1967).

7. A. M. SIEGAL, H. W. CASEY, R. W. BOWMAN, J. E. TRAYNOR, "Leukemia in a Rhesus Monkey (Macaca Mulatta) Following Exposure to Whole-Body Proton Irradiation," *Blood*, **32**, 989 (1986).

8. H. W. CASEY, P. S. COOGAN, J. E. TRAYNOR, "Late Effects of 32-MeV Proton Irradiation in Primates," *Radiat. Res.*, **39**, 634 (1969).

9. J. E. TRAYNOR, H. W. CASEY, "Five-Year Follow-Up of Primates Exposed to 55-MeV Protons," *Radiat. Res.*, **47**, 143 (1971).

10. J. H. KIRK "Body Weight Decreases in Some Proton Exposed Primates," *Space Life Sci.*, **3**, 271 (1971).

11. W. F. MacKENZIE, G. A. SPLITTER, M. G. VALERIO, "Endometriosis in Primates," *Medical Primatology, Proc. 3rd Conf. Experimental Medicine and Surgery of Primates*, Lyon, 1972, p. 288, E. E. GOLDSMITH, J. MOOR JANOWSKI, Eds.

12. G. A. SPLITTER, J. J. KIRK, W. F. MacKENZIE, C. A. RAWLINGS, "Endometriosis in Four Irradiated Rhesus Monkeys," *Vet. Pathol.*, **9**, 249 (1972).

13. J. H. KRUPP, "Nine-Year Mortality Experience in Proton-Exposed Macaca Mulatta," *Radiat. Res.*, **67**, 244 (1976).

14. D. H. WOOD, M. G. YOCHMOWITZ, Y. L. SALMON, R. A. BOSTER, R. L. EASON, "Proton Irradiation and Endometriosis," *Aviat. Space Environ. Med.*, **54**, 718 (1983).

15. M. G. YOCHMOWITZ, D. H. WOOD, Y. L. SALMON, "Seventeen-Year Mortality Experience RF Proton Radiation in Macaca Mulatta," *Radiat. Res.*, **102**, 14 (1985).

16. D. H. WOOD, M. G. YOCHMOWITZ, K. A. HARDY, Y. L. SALMON, "Occurrence of Brain Tumors in Rhesus Monkeys Exposed to 55-MeV Protons," Pergamon Press (to appear in *Advances in Space Research*).

17. J. C. MITCHELL, G. V. DALRYMPLE, G. H. WILLIAMS, J. D. HALL, I. L. MORGAN, "Proton Depth-Dose Dosimetry," *Radiat. Res.*, **28**, 390 (1966).

18. G. H. WILLIAMS, J. D. HALL, I. L. MORGAN, "Whole-Body Irradiation of Primates with Protons of Energies to 400-MeV," *Radiat. Res.*, **28**, 372 (1966).

3. Development of Effective Chemical Protectors Against Radiation, *Lawrence Fleckenstein (Walter Reed), invited*

INTRODUCTION

Since 1959, interrupted during the early 1970s for ~10 yr, the U.S. Army Medical Research and Development Command has sponsored an Antiradiation Drug Development Program. The objective of the program is to develop a drug or combination of drugs that could be taken by military personnel or civilian populations to protect them from the effects of ionizing radiation from nuclear weapons. Emphasis is placed on the development of an orally effective radioprotective drug. The present overall drug development effort includes chemical synthesis, animal efficacy screening in mice, determination of physical chemical properties, dosage form development, pharmacokinetic, drug metabolism, and pharmacologic testing. During the program, ~6000 compounds have been chemically synthesized and tested for efficacy. Only a few compounds have been tested in larger animals. At the present time, the only animal efficacy model is for mice.

Since the early 1980s, the program has become more narrowly focused, concentrating on following existing leads, principally aminothiol compounds. Synthesis of new compounds is concentrated in the areas of alternative thiol covering functions, variations of aminothiol structure, and nonamino radioprotectants. Ethiofos(WR 2721), S-2-(3-aminopropylamino)ethyl phosphorothioic acid is the prototype aminothiol radioprotectant and has been most extensively studied. Ethiofos is currently the only radioprotectant with an active "investigational new drug application"; however, several related phosphorothioates compounds have also been identified as possible candidates for development. Administered intravenously, ethiofos protects mice, dogs, and rhesus monkeys against the lethal effects of X rays and gamma radiation.[1] Oral dosing of the drug fails to protect dogs or monkeys, suggesting poor bioavailability. Various formulation approaches, including microencapsulation, have been investigated to improve oral absorption.[2]

DESCRIPTION

Studies have been undertaken to define the mechanism of poor oral bioavailability of ethiofos. *In vitro* hydrolysis experiments indicate the drug is unstable at the gastric pH (Ref. 2). It has recently been shown that ethiofos suppresses stomach emptying and motility in the rhesus monkey.[3] Detailed pharmacokinetic studies have been carried out in the rhesus monkey to define the absorption of the drug.[4] In a series of experiments, ethiofos and ^{14}C-labeled ethiofos have been administered by various routes of administration (intravenous, intraduodenal, and by infusion into the ileocecal vein). Plasma ethiofos and major metabolite levels were determined by specific high-phase liquid chromatography analysis to follow the disposition of the drug.

RESULTS

Pharmacokinetic experiments in the monkey have shown the drug is absorbed from the intestinal tract, but the drug is highly metabolized during absorption. This metabolism occurs at the level of the intestinal wall and the liver. As a result, drug levels of ethiofos and the active thiol metabolite are extremely low in the systemic circulation following oral administration.

Efforts to develop an oral dosage form of ethiofos have centered around microencapsulation of the drug. Formulation factors can be altered to vary the site and rate of drug delivery in the gastrointestinal tract. Microencapsulation is designed to protect the drug from acid hydrolysis in the stomach and release the drug at the site of absorption in the small intestine. However, microencapsulation will not overcome the problem of "first-pass" removal of the drug by metabolism during absorption. Efforts to overcome this metabolism have centered on identifying alternative phosphorothioate compounds not subject to this problem. Another approach under investigation is the synthesis of chemical derivatives (prodrugs), which are well absorbed and can be converted under the influence of biological fluids or enzymes to an active radioprotectant. Saturation or competition for the enzymes responsible for first-pass removal of the drug is currently under study as an alternative means of overcoming this problem. Circumventing the removal of ethiofos by metabolism during absorption