ATGP copy

AFRRI SR74-23
OCTOBER 1974

AFRRI
SCIENTIFIC
REPORT

AFRRI SR74-23

POSTIRRADIATION VOMITING

G. R. Middleton
R. W. Young

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

AFRRI SR74-23
October 1974

POSTIRRADIATION VOMITING

G. R. MIDDLETON
R. W. YOUNG

John W. Cable
JOHN W. CABLE
Lieutenant Colonel, USAF, VC
Chairman
Behavioral Sciences Department

Myron I. Varon
MYRON I. VARON
Captain MC USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

ACKNOWLEDGMENT

The authors wish to acknowledge the technical assistance of J. R. Harrison, G. G. Kessell and P. Mannon.

TABLE OF CONTENTS

LIST OF FIGURES

TABLES

FOREWORD
(Nontechnical summary)

Vomiting has been observed in supralethally irradiated subjects shortly after exposure to ionizing radiation and again as a symptom of terminal radiation sickness prior to death. The later stage of vomiting has been described in lethality studies, but data concerning the initial phase of vomiting are sparse. The purpose of this study was to determine the relationship between radiation dose and occurrence of vomiting during the first 2 hours postirradiation. Data from 129 rhesus monkeys exposed to radiation doses ranging from 700 to 5600 rads were analyzed for incidence of vomiting. The number of animals vomiting and total number of vomitions followed a similar pattern. Below 1000 rads both parameters increased directly with dose, while at higher doses they decreased with increasing dose. Most of the vomiting episodes at all dose levels occurred between 20 and 50 minutes after exposure to the radiation.

ABSTRACT

One hundred and twenty-nine male rhesus monkeys (Macaca mulatta) exposed to prompt radiations (neutron/gamma = 0.4 and pulse width = 50 msec) ranging from 700 to 5600 rads (midhead dose) were analyzed for incidence of vomiting. The animals were fasted 18 hours preexposure and observed for incidence of vomiting for 2 hours postexposure. For doses less than 1000 rads, the number of animals that vomited increased directly with dose. Above 1000 rads, the number of animals that vomited decreased with increasing dose. The total number of vomitions per dose group followed a nearly identical pattern to the incidence of emesis. In all dose groups most of the emetic episodes occurred between 20 and 50 minutes postirradiation.

I. INTRODUCTION

Vomiting is one of the characteristic symptoms of radiation sickness. This finding is based on both clinical[15] and experimental observations.[3,4,7,9] Vomiting produced by a single lethal dose of high-energy radiation occurs in two distinct phases, the first occurs almost immediately after exposure and the second, which is associated with terminal radiation sickness, occurs days to weeks later. The later phase of vomiting has been described in some detail in reports of lethality studies,[5,7,9] but data concerning early postirradiation vomiting are sparse. Chinn and Wang[4] present emesis data for sublethal and lethal radiation doses for the dog, but little else is to be found in the literature.

Anatomical dependence of emesis has been linked to different sites and pathways by several investigators. Work by Chinn et al.[3,4] implicated zones in the medulla oblongata and reticular formation in radiation-induced emesis. However, Borison[1] and Brizzee[2] showed that these zones may be merely interposed in the afferent pathway of the reflex for radiation-induced emesis. They observed complete inhibition of radiation-produced vomiting in both the cat[1] (at 5500 rads) and the monkey[2] (at 1200 rads) following supradiaphragmatic vagotomy. It has been shown that vomiting occurs after gut denervation or even abdominal evisceration[2,5] so that the vagotomy itself was not the cause of emesis inhibition. These results imply a central nervous system involvement in the emetic response to radiation. However, no useful dose response relationship exists for emesis associated with supralethal irradiation, despite the CNS implications in emesis.

Lethality studies have noted the rapid onset of emesis after irradiation but do not agree on its relative incidence. This apparent lack of agreement may stem from differences in pertinent experimental variables between the studies currently in the literature. Dose rate and species differences are well-known sources of variation between studies of radiation effects and must be considered here. Additionally, in the study of vomiting, control of food intake during the hours prior to exposure is needed for the detection and relative incidence of emesis to be meaningful.[10,15] The purpose of this study was to determine, during the first 2 hours postirradiation, a dose response relationship between pulsed supralethal radiation and emesis in the rhesus monkey under controlled feeding conditions.

II. METHODS

One hundred and twenty-nine male rhesus monkeys (Macaca mulatta) ranging in age from 1.3 to 4.2 years and weighing between 2.0 and 5.3 kg were studied. The animals were restrained in primate chairs and were trained to a simple visual discrimination behavioral paradigm. The behavioral performance data from these animals are reported elsewhere.[14] Prior to irradiation, the last feeding occurred 18 hours before irradiation and consisted of 1 cup of Purina Monkey Chow.

The monkeys were irradiated in a pulsed (50 msec full width at half maximum) mixed neutron-gamma field ($n/\gamma = 0.4$) from the AFRRI-TRIGA Mark-F reactor.[6] Each animal was 125 cm from the vertical center line of the reactor core. Animals were exposed to seven dose levels: 763, 933, 1159, 1826, 2705, 3773, and 5258 rads (midhead doses). The average age in years and weight in kilograms (in parentheses) of the respective dose groups were 2.6 (3.3), 2.1 (3.2), 2.4 (3.2), 2.4 (3.3), 2.4 (3.7), 2.1 (3.3), and 2.2 (3.5).

The animals were observed visually via a closed circuit television system for emesis for 2 hours postirradiation. Emesis criteria required that the monkey regurgitate substance from his mouth. Unusual swallowing or nonproductive retching was not deemed to constitute emesis.

III. RESULTS

Emesis incidence, the number of animals experiencing emesis in the first 2 hours postirradiation, is presented in Figure 1. The percentage of animals vomiting

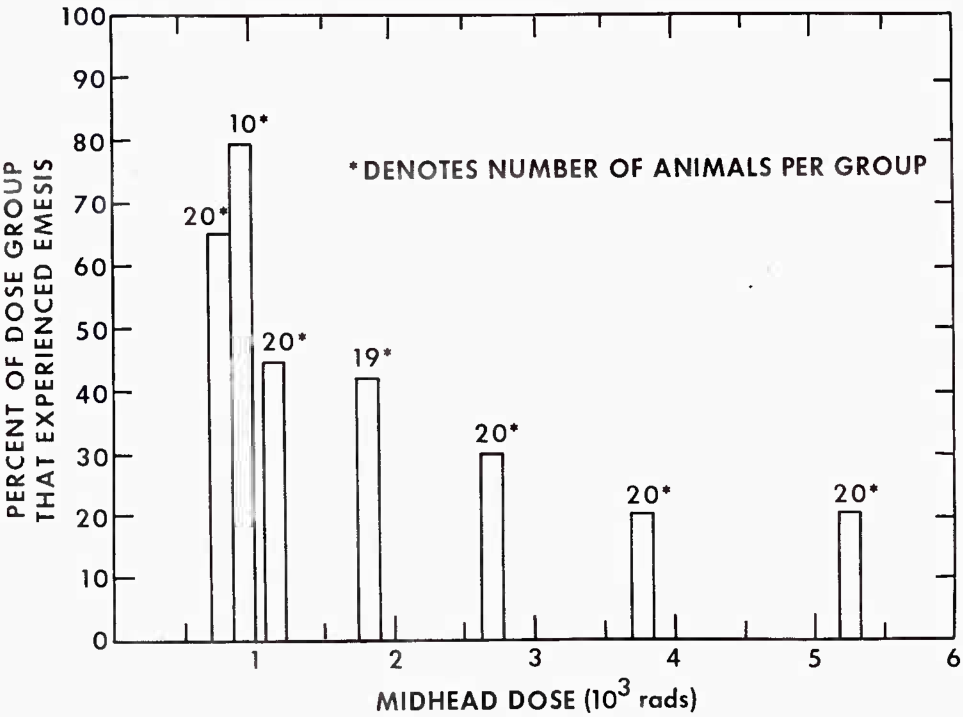

Figure 1. Incidence of emesis in the rhesus monkey after pulsed whole-body irradiation

increased with dose up to 1000 rads. Above 1000 rads, emesis incidence decreased with increasing dose.

Total emesis, the total number of vomitions by all animals, and the times of their occurrence are presented by dose group in Figures 2 and 3. Total emesis occurrence is presented in Figure 2 as average number of vomitions to take into account the different number of animals per group. It followed a pattern nearly identical to that of

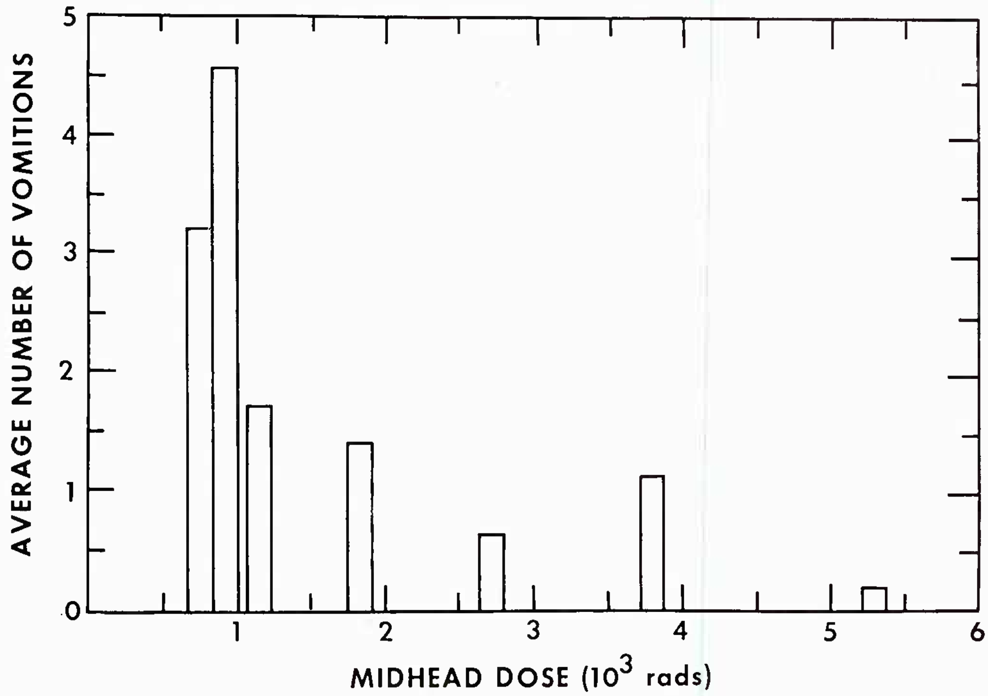

Figure 2. Total vomition occurrence in the rhesus monkey after pulsed whole-body irradiation

emesis incidence, with the exception of the 3700-rad group. The difference in the 3700-rad group was not significant (unpaired t-test). The time course of the emesis episodes (Figure 3) is also described by a biphasic function. The first appearance of

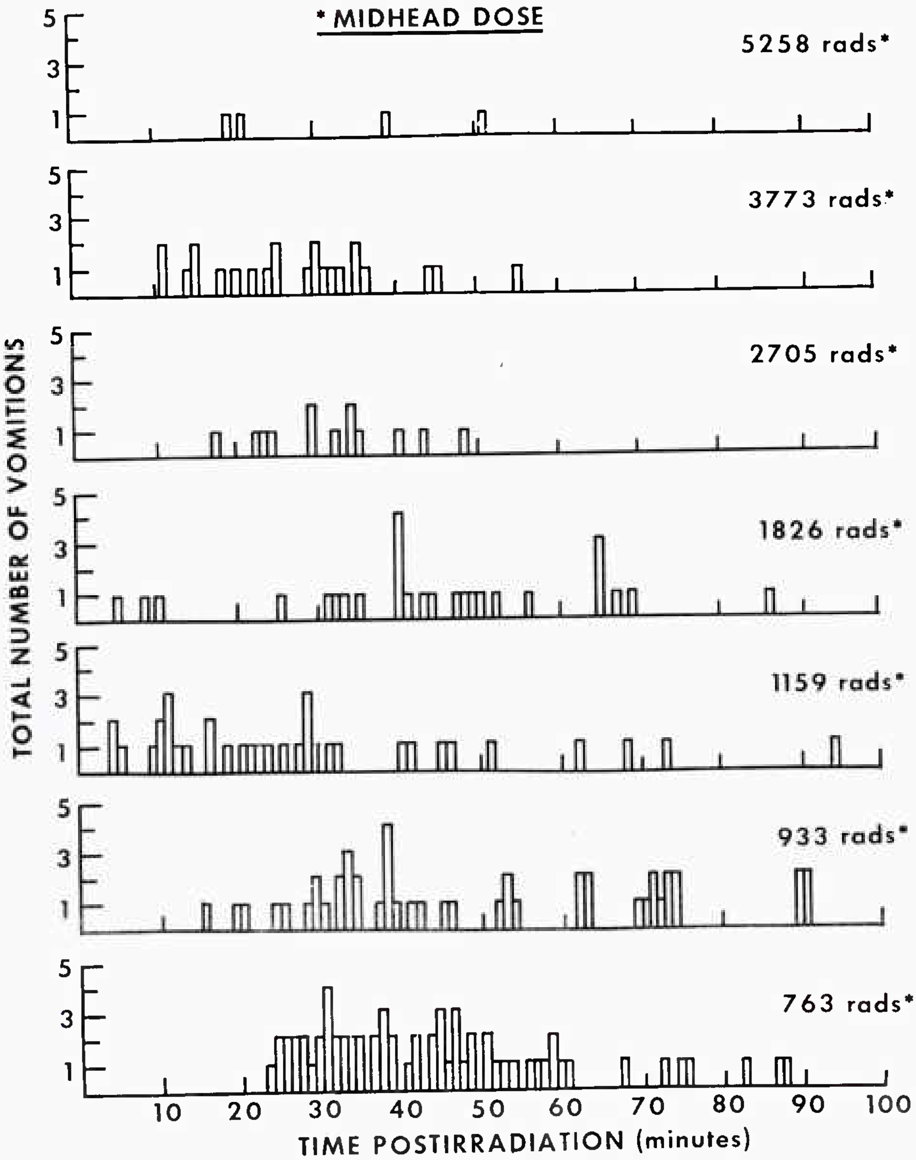

Figure 3. Time distribution of total vomition episodes in the rhesus monkey after pulsed whole-body irradiation

vomiting occurred at progressively shorter intervals following exposures as doses increased up to 2000 rads. Below 2000 rads, vomiting was observed as early as 4 minutes after exposure. Above 2000 rads, no emesis occurred before 12 minutes. In all of the groups, most of the vomiting occurred in the 20- to 50-minute interval postirradiation.

Individual test subject data are given in the appendix.

IV. DISCUSSION

All of the implications of the emesis occurrence distributions are not clear at this point. However, the shapes of the emesis incidence curves and a comparison of the emesis and behavioral performance data do yield some information concerning the dose dependency of the emesis mechanism and its relationship to the incapacitation that typically follows exposure to supralethal radiation.

The slopes of the dose-response curves reveal the general dose dependency of emesis. At or below lethal doses, data from irradiated dogs[4] (13 r/min) and human clinical experience[12] indicate that increased radiation dose produces a higher incidence of vomiting. Although the data from the lowest two dose groups (Figures 1 and 2) in this study are not statistically different* they tend to support these previous findings. A positive slope at these lower dose levels implies some type of excitation or stimulation of the vomiting mechanism.

At doses in excess of 1000 rads, the slope of the emesis incidence curves becomes negative, implying some inhibition or lessening of the radiation-induced emetic effect. Large supralethal doses of radiation may interfere with the transmission or reception of afferent vagus impulses from injured organs, which are thought to play some part in radiation-induced emesis.[1, 2] At lower doses, the radiation may serve to potentiate the emetic response by lowering the threshold of the emetic centers so

---

* Fisher's exact probability test, Nonparametric Statistics for the Behavioral Sciences, S. Siegel. New York, N. Y., McGraw-Hill Book Company, Inc., 1956.

that stimuli usually incapable of invoking vomiting may then do so. This would be analogous to the situation in pharmacology where one may see paradoxical results with different doses of barbiturates.[8] A reversal in the emesis response to irradiation was previously not anticipated.[11,12]

Additionally, human data from nuclear accident victims and therapeutic experience with cancer patients at low dose rates have indicated a much longer latent period (several hours) from exposure to onset of emesis.[11] The importance of preexposure fasting has previously been noted, and the complicating factors of dosimetry in the accident cases and concurrent signs and symptoms of their disease and the effects of other therapy in the therapeutic data may explain this difference. This explanation seems preferable to accounting for the later onset of vomiting solely on the basis of species difference.

Besides the inferences which can be derived from the emesis data alone, a comparison of the emesis data with the results of visual discrimination testing of these animals indicates a probable relationship between emesis and behavioral incapacitation. For example, at 3700 rads, with one exception, those animals that vomited did not exhibit behavioral incapacitation. Over the entire range of doses studied, 19 of 20 animals that did not recover from the incapacitation did not vomit. The one animal that vomited only did so once. This trend suggests a relationship between the absence of emesis and permanent incapacitation. This hypothesis is further supported by the data from previously reported irradiation of five monkeys with 10,000 rads.[13] In that study, the three animals that did not vomit did not recover from behavioral incapacitation. The two that vomited recovered from the incapacitation.

The relationship between vomiting and incapacitation raises the question of a physiological connection between postirradiation emesis and incapacitation. The specific act of vomiting does not seem to produce any contiguous adverse or beneficial effect upon the performance of this visual discrimination task. Contrary to what might be expected,[11] animals performing the task did not demonstrate any significant deviation in performance immediately before, during, or after an emesis episode. Whether potentiating or eliminating the emesis episodes might enhance the ability of an animal to perform a task at some later time after irradiation is not known.

In addition to the data indicating that vomiting is absent in those animals that are permanently incapacitated by supralethal irradiation, there is evidence that the initial time of occurrence of emesis is related to the overall incidence of postexposure incapacitation. As radiation doses increased up to 2000 rads the first emesis episodes occurred at shorter intervals after exposure (Figure 3). Above 2000 rads the time of emesis onset was not a function of dose. The dose-response curve for severe degradation of visual discrimination performance[14] was likewise biphasic with an inflection point at 2000 rads. The reason for this similarity in response is as yet unknown. The specific mechanisms behind these relationships are not known, but the current data indicate that emesis episodes and severe degradation of performance after exposure to supralethal doses of radiation may be in some way related.

REFERENCES

1. Borison, H. L. Site of emetic action of X-radiation in the cat. J. Comp. Neurol. 107:439-453, 1957.

2. Brizzee, K. R. Effect of localized brain stem lesions and supradiaphragmatic vagotomy on X-irradiation emesis in the monkey. Am. J. Physiol. 187: 567-570, 1956.

3. Chinn, H. I. and Sheldon, G. L. Effect of chlorpromazine on emesis after radiation. Proc. Soc. Exptl. Biol. Med. 86:293-295, 1954.

4. Chinn, H. I. and Wang, S. C. Locus of emetic action following irradiation. Proc. Soc. Exptl. Biol. Med. 85:472-474, 1954.

5. Conard, R. A. Some effects of ionizing radiation on the physiology of the gastrointestinal tract: a review. Radiation Res. 5:167-188, 1956.

6. Dowling, J. H. Experimental determination of dose for the monkey in a reactor pulse environment. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Scientific Report SR66-3, 1966.

7. Eldred, E. and Trowbridge, W. V. Radiation sickness in the monkey. Radiology 62:65-73, 1954.

8. Goodman, L. S. and Gilman, A., editors, 3rd ed. The Pharmacological Basis of Therapeutics. New York, N. Y., The Macmillan Company, 1965.

9. Henschke, U. K. and Morton, J. L. Mortality of rhesus monkeys after single total body irradiation. Am. J. Roentgenol. Radium Ther. Nucl. Med. 77:899-909, 1957.

10. Kimeldorf, D. J. and Hunt, E. L. Ionizing Radiation: Neural Function and Behavior. New York and London, Academic Press, 1965.

11. Langham, W. H., editor. Radiobiological Factors in Manned Space Flight. Washington, D. C., National Academy of Sciences - National Research Council Publication 1487, 1967.

12. Lushbaugh, C. C., Comas, F., Saenger, E. L., Jacobs, M., Hofstra, R. and Andrews, G. A. Radiosensitivity of man by extrapolation from studies of total-body irradiation of patients. Radiation Res. 27:487-488 (Abstract), 1966.

13. Thorp, J. W. and Young, R. W. Monkey performance after partial body irradiation. Aerospace Med. 42:503-507, 1971.

14. Young, R. W. and Middleton, G. R. The incidence of behavioral incapacitation in the monkey (Macaca mulatta) as a function of pulsed whole-body gamma-neutron radiation dose. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Annual Research Report ARR-7, 1 July 1972 - 30 June 1973.

15. Zugerman, I. Early reactions following roentgen ray epilations. Arch. Derm. Syph. 60:722-725, 1949.

APPENDIX

Test Subject Data

GROUP 1

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD*	MTD†	FIA‡			
F2-43	675	631	819	2.0	3.6	No
F2-49	675	631	819	3.3	3.4	Yes
B2-62	702	656	852	1.7	2.8	Yes
B2-65	702	656	852	2.0	3.0	No
F2-56	748	699	908	2.9	4.1	No
F2-57	748	699	908	3.0	3.6	Yes
C2-12	770	719	935	2.2	3.4	Yes
C2-66	770	719	935	2.2	3.6	Yes
B2-72	774	723	940	2.7	3.4	Yes
B2-69	774	723	940	1.8	2.8	No
F2-52	780	729	947	3.4	4.1	Yes
F2-55	780	729	947	3.4	3.6	Yes
G2-3	780	729	947	2.8	2.7	Yes
F2-46	780	729	947	2.2	3.2	Yes
FI-53	800	748	972	2.5	2.6	Yes
A2-51	800	748	972	2.5	3.0	Yes
A2-10	800	748	972	3.8	3.2	No
C2-27	800	748	972	2.5	3.6	No
C2-76	800	748	972	1.8	3.2	Yes
GI-24	802	750	974	2.8	3.0	No
Mean	763	713	926	2.6	3.3	13/20

* MHD = Midhead dose
† MTD = Midline tissue dose = .935 MHD
‡ FIA = Free-in-air dose = 1.215 MHD

GROUP 2

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
H3-31§	900	841	1093	2.7	2.0	Yes
H3-33§	900	841	1093	2.7	3.2	Yes
C2-58	900	841	1093	1.5	3.2	No
C2-71	900	841	1093	1.3	2.7	Yes
C2-10	900	841	1093	2.2	3.6	Yes
C2-64	900	841	1093	2.6	3.6	Yes
11	975	911	1185	1.6	3.0	Yes
C2-46	975	911	1185	2.3	4.1	Yes
13	990	925	1203	1.6	3.4	Yes
D-17	990	925	1203	2.2	3.0	No
Mean	933	871	1132	2.1	3.2	8/10

§ Naive subjects

GROUP 3

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
HI-55	1075	1005	1306	2.3	3.0	No
FI-21	1100	1028	1336	2.4	3.4	No
GI-52	1100	1028	1336	2.3	3.4	No
GI-62	1100	1028	1336	2.4	3.2	No
GI-55	1130	1056	1373	2.6	3.6	Yes
HI-65	1134	1060	1378	2.3	3.0	Yes
FI-3	1138	1064	1383	2.3	2.8	Yes
FI-10	1138	1064	1383	2.3	3.2	Yes
A2-73	1145	1070	1391	2.2	3.4	No
HI-43	1150	1075	1397	3.0	3.1	No
A2-80	1150	1075	1397	2.8	3.6	No
GI-67	1150	1075	1397	3.0	3.0	Yes
FI-12	1188	1110	1443	2.3	3.6	Yes
FI-31	1188	1110	1443	1.8	3.2	No
GI-13	1200	1121	1458	1.9	3.0	No
HI-29	1200	1122	1459	2.6	3.2	Yes
FI-19	1201	1122	1459	2.8	3.2	No
FI-54	1201	1122	1459	2.3	3.6	Yes
J3	1214	1135	1475	2.2	2.4	No
W25	1214	1135	1475	2.0	2.4	Yes
Mean	1159	1083	1408	2.4	3.2	9/20

GROUP 4

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
HI-41	1737	1623	2110	2.3	3.4	No
GI-21	1752	1637	2129	2.3	3.0	Yes
FI-37	1777	1661	2159	2.2	3.0	Yes
HI-7	1777	1661	2159	2.8	2.8	No
GI-8	1778	1662	2160	2.3	2.8	No
A2-37	1780	1664	2163	2.0	3.4	No
171	1820	1701	2211	2.0	4.4	Yes
213	1820	1701	2211	2.5	2.9	Yes
214	1820	1701	2211	2.5	3.3	Yes
218	1820	1701	2211	2.5	2.9	No
226	1820	1701	2211	2.5	2.7	Yes
230	1820	1701	2211	2.5	3.4	No
240	1820	1701	2211	1.5	3.5	Yes
244	1820	1701	2211	2.0	3.7	No
HI-9	1850	1729	2248	3.0	3.4	No
217	1916	1791	2328	2.5	3.6	No
222	1916	1791	2328	2.5	3.4	Yes
216	1927	1801	2341	2.5	2.5	No
227	1927	1801	2341	2.5	3.6	No
Mean	1826	1707	2219	2.4	3.3	8/19

GROUP 5

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
803	2436	2277	2960	3.5	4.4	No
164	2591	2421	3148	1.5	4.1	No
818	2591	2421	3148	2.6	2.9	Yes
228	2591	2421	3148	2.5	3.3	Yes
817	2591	2421	3148	1.6	2.9	No
149	2695	2519	3274	2.4	5.3	No
151	2695	2519	3274	2.4	5.2	No
176	2695	2519	3274	1.5	3.7	No
59	2695	2519	3274	2.2	3.4	Yes
63	2695	2519	3274	2.2	4.2	Yes
245	2746	2566	3336	1.3	3.6	No
B-17	2746	2566	3336	3.0	3.2	Yes
B-23	2746	2566	3336	1.5	3.2	Yes
250	2799	2616	3401	2.5	3.6	No
254	2799	2616	3401	1.5	3.9	No
268	2799	2616	3401	1.5	3.5	No
304	2799	2616	3401	1.5	3.1	No
31	2799	2616	3401	4.0	3.8	No
20	2799	2616	3401	4.2	3.8	No
25	2799	2616	3401	3.9	3.6	No
Mean	2705	2528	3286	2.4	3.7	6/20

GROUP 6

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
C2-9	3670	3430	4459	1.4	2.7	Yes
C2-78	3670	3430	4459	2.4	3.6	Yes
A2-62	3681	3440	4472	3.3	3.3	No
A2-9	3700	3458	4495	2.3	3.2	No
A2-17	3700	3458	4495	3.0	3.0	No
B2-68	3700	3458	4495	1.8	3.4	No
B2-48	3700	3458	4495	2.1	3.3	No
C2-57	3700	3458	4495	1.7	3.4	Yes
B2-70	3709	3466	4506	2.0	3.4	No
B2-74	3709	3466	4506	2.2	2.7	No
A2-71	3744	3499	4549	3.4	3.4	No
B2-5	3744	3499	4549	1.8	3.3	No
C2-30	3764	3518	4573	1.5	3.2	No
C2-80	3764	3518	4573	1.8	2.7	No
C2-45	3800	3551	4617	2.0	3.6	No
C2-70	3800	3551	4617	2.0	3.9	No
10	3800	3551	4617	1.9	3.9	No
14	3800	3551	4617	1.9	3.2	No
C2-23	4150	3879	5042	1.8	3.4	No
C2-73	4150	3879	5042	2.2	3.4	Yes
Mean	3773	3526	4584	2.1	3.3	4/20

GROUP 7

Animal #	Dose (rads)			Age (years)	Weight (kg)	Emesis
	MHD	MTD	FIA			
781	4816	4501	5851	3.0	3.6	Yes
768	4816	4501	5851	2.5	3.4	Yes
785	4816	4501	5851	2.5	3.2	Yes
780	5030	4701	6111	3.0	3.8	Yes
778	5138	4802	6242	2.5	3.5	No
40	5190	4850	6306	2.7	3.9	No
D-15	5200	4860	6318	1.7	3.2	No
27	5200	4860	6318	1.9	2.7	No
1	5245	4902	6372	1.5	3.5	No
9	5245	4902	6372	2.0	3.4	No
12B	5300	4953	6438	1.7	3.0	No
D-13	5300	4953	6438	2.2	3.9	No
B-27	5352	5002	6502	2.5	3.6	No
C-12	5352	5002	6502	2.0	3.3	No
291	5459	5102	6632	2.0	3.3	No
12A	5459	5102	6632	3.0	3.6	No
C33	5566	5202	6762	3.5	4.0	No
33	5566	5202	6762	1.5	3.8	No
48	5566	5202	6762	1.5	3.5	No
C27	5566	5202	6762	1.5	3.6	No
Mean	5258	4915	6389	2.2	3.5	4/20

UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)* Armed Forces Radiobiology Research Institute Defense Nuclear Agency Bethesda, Maryland 20014	2a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED 2b. GROUP N/A

3. REPORT TITLE

POSTIRRADIATION VOMITING

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*

5. AUTHOR(S) *(First name, middle initial, last name)*

G. R. Middleton and R. W. Young

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
October 1974	19	15

8a. CONTRACT OR GRANT NO. b. PROJECT NO. NWED QAXM c. Task and Subtask A 904 d. Work Unit 02	9a. ORIGINATOR'S REPORT NUMBER(S) AFRRI SR74-23 9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Director Defense Nuclear Agency Washington, D. C. 20305

13. ABSTRACT

One hundred and twenty-nine male rhesus monkeys (Macaca mulatta) exposed to prompt radiations (neutron/gamma = 0.4 and pulse width = 50 msec) ranging from 700 to 5600 rads (midhead dose) were analyzed for incidence of vomiting. The animals were fasted 18 hours preexposure and observed for incidence of vomiting for 2 hours postexposure. For doses less than 1000 rads, the number of animals that vomited increased directly with dose. Above 1000 rads, the number of animals that vomited decreased with increasing dose. The total number of vomitions per dose group followed a nearly identical pattern to the incidence of emesis. In all dose groups most of the emetic episodes occurred between 20 and 50 minutes postirradiation.

DD FORM 1473 1 NOV 65

UNCLASSIFIED
Security Classification