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CLINICAL STUDIES OF RADIATION EFFECTS IN MAN: A Preliminary Report of a Retrospective Search for Dose-Response Relationships in the Prodromal Syndrome.[1,2]

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The effects of total-body irradiation on man have been studied clinically for about 70 years or since Walsh (1) first described "radiation sickness" in 1897. Thus it is well-known that exposure to ionizing radiations can cause a man to become so ill that sometime later he cannot work. The dose-response relationships are, however, poorly known (2,3) and present estimates are based largely upon conjectures derived by extrapolation from animal experiments (3) or from experience with radiation accident victims (4-9), atomic bomb casualties (3, 10-12) and therapeutically irradiated patients (1-3, 13-16). Because these estimates are all we have, necessity has dictated their use in planning for civilian defense, radiotherapy, and occupational medicine, but everyone will agree that they are not sufficiently accurate to allow predicting the probability of sublethal doses of radiation causing deleterious functional effects that might lead to sudden or delayed decrements in performance capabilities (2). In developing the Estimated Residual Dose (ERD) concept upon which most occupational, and civilian defense medical plans are based today (18-20), the ERD Committee was not then faced with considering a form of radiation sickness so mild that medical care was not immediately required but severe enough to cause performance failure that could result in death. Although most clinicians will agree with the Committee's conclusion that nine out of ten persons exposed to less than 200 R would not require medical care, little cheer for space-flight planners is contained in the conclusion that 75 R is the smallest dose that would cause vomiting in 10% of a human population,when the Committee's confidence in this opinion was only $\pm$ 25%. Obviously (2) more accurate dose-response relationships for man are needed before the success

or failure of a manned space flight can be predicted with the use of probability equations for determining the chances that some form of radiation sickness will occur after exposure to a finite dose of radiation.

At present it is not known with certainty how often the symptoms and signs of the prodromal radiation syndrome - anorexia, nausea, vomiting, diarrhea, listlessness (apathy) and increased fatigability - would lead to delayed or lowered performance capabilities, but it seems more justifiable to assume that they would than that they would not (2). Also, from previous clinical studies (11-17) the prodromal syndrome is known to occur after a short latent period of 2 to 6 hours, with a peak frequency of about 3 hours; to be self limiting, usually within 48 hours, even at supralethal total-body doses, and to vary in severity not only in respect to dose but also in respect to individual susceptibility (2). Although positive assumptions are usually made, other stresses have never actually been shown to augment the production of these responses by irradiation, nor good health, in itself, to decrease them. So from these points of view, it would seem that the prodromal syndrome probably constitutes the earliest physiologic threat at the clinical level to man's continued performance during and shortly after irradiation. For these reasons and because the hematologic and immunologic failures of the acute radiation syndrome are comparatively delayed, it was decided to concentrate upon determining directly the dosage relationships of the earlier clinically demonstrable effects of tha prodromal syndrome. Previous similar studies (12,17) have not attempted to derive the effective dose for eliciting these responses (ED_{50}) because dosages or observations were not reliable or not sufficiently numerous for statistical purposes.

The studies described here are then a preliminary attempt to obtain probit equations of radiation dose-symptomatic response relationships for the six commonest symptoms of the prodromal radiation syndrome - anorexia, nausea, vomiting, diarrhea, fatigue, and listlessness. An attempt was also made to determine the 60-day postirradiation LD_{50} of this group of patients in order to provide an upper (lethal) frame of reference to the ED_{50} for these sublethal effects. The studies were planned so that the 95% confidence intervals in the measurements would be obtained in order to define the statistical uncertainties (21).

The 93 patients who had been irradiated for therapeutic purposes in the Oak Ridge Institute of Nuclear Studies (ORINS) (22,23) total-body irradiation facility (Fig. 1) and 7 nuclear radiation accident victims who were treated at the ORINS Medical Division (6,8) comprised the 100 cases studied. Additional case studies of total-body irradiation (approximately 700) have been obtained from other hospital centers and are in the process of being included in the second phase of this study. All the ORINS patients had either an inoperable malignancy or a blood dyscrasia for which they had previously been treated by conventional means; the disease was in relapse at the time of their exposure. A 3-day period of study preceded the single radiation exposure. Eighty-four patients were exposed to 50, 100, or 300 R of cesium-137 gamma radiation, at the rate of 0.75 to 1.6 R/minute. Nine others were exposed to opposing-beam irradiation with cobalt-60. Seven of the study cases were normal men accidentally exposed in a nuclear criticality incident. After radiation exposure, clinical and laboratory observations were made for a period of 6 weeks during which the therapeutically irradiated

persons did not receive other therapy unless the condition of the patient demanded abandoning the study. The clinical dosimetry was done using compartmentalized water phantoms (Fig. 2), Victoreen ratemeters, and the aqueous ferrous sulfate system (Fricke dosimeter) (23). The dosages of the 7 accident cases were determined by a mock-up of the accident at the site as previously reported (24). To relate the absorbed dose from exposure to the different kinds of radiations to an acceptable standard unit, the midline air dose and the first collision doses in the neutron exposures were converted to midepigastric rads (Fig. 2) on the basis of the depth-dose measurements for cesium-137 and cobalt-60 (23), and appropriate quality factors for neutrons and gamma rays from critical excursions (24). The resulting 100 midepigastric doses were found to be clustered in 4 groups of unequal numbers of cases. The arithmetic and geometric means of each group were used respectively for the subsequent linear and logarithmic line fitting programs (21).

An encodement was made of symptoms, signs, and laboratory and nursing observations, which enabled pertinent information from the clinical chart to be extracted for the 6 weeks following exposure and coded digitally by trained clerical personnel. Physicians were not allowed to decide intuitively or otherwise whether a recorded symptom or sign was or was not related to radiation exposure, although it was well-known that some of these patients were exhibiting them without radiation. The coded observations were arranged and stored on magnetic tape and programs were devised for data retrieval. Seven quantal clinical responses - anorexia, nausea, vomiting, diarrhea, fatigue, listlessness, death - were studied. Systems were

developed for each symptom or sign that enabled the computer to determine from the encoded data whether or not each of these seven responses occurred during prescribed postirradiation periods in each case. The percentage of responders per dosage group was determined and a probit analysis of linear dose-response and log dose-response relationships was performed. The chi-square goodness-of-fit of the resulting regression lines and the 95% confidence limits were then obtained.

Results

The incidence of only five of the six prodromal responses was determinable because the existence of listlessness or apathy was not noted in these data a sufficient number of times to enable it to be studied quantally. The incidence of anorexia, nausea, and vomiting are shown in Table IA. As quantal responses, these three symptoms and signs were defined as occurring or not during the first 48 hours postirradiation, even though in most instances the effect occurred within the first 6 hours after exposure. The apparent practice of clinical and nursing staffs as well as the patients themselves to not report or record nausea if vomiting occurred and to not report or record anorexia if nausea occurred, forced the acceptance of the clinical notion that these responses are 3 degrees of gastrointestinal distress rather than 3 separate or unrelated symptoms. Therefore, the number of persons in this study experiencing anorexia consists of those who refused their meals, or were nauseated, or vomited; and nausea consists of those who were nauseated or vomited. The 100% incidence of anorexia in the highest dosage group required the use of a correction factor in the use of this data point in the probit analyses (21).

TABLE IA

Frequency of anorexia, nausea, and vomiting in single radiation exposure of therapeutic and accident patients of ORINS Medical Division.

Mean Dose (Rad)	Total Cases	Anorexia Yes	Anorexia %	Nausea Yes	Nausea %	Vomiting Yes	Vomiting %
31.7	30	5	17	4	13	2	7
65.2	38	16	42	11	29	8	21
187.5	22	21	95	17	77	15	68
303.8	10	10	100	8	80	7	70

The incidence of fatigue, diarrhea, and death are shown for the 4 dosage groups in Table IB, as the quantal response during the entire 42-day postirradiation observation period. An attempt to confine the quantal measurement of occurrence of fatigue and diarrhea to the first 48 hours after irradiation revealed that these symptoms occurred during the first 48 hours only in the highest dosage group, an observation well-supported by many previously reported studies of supralethally irradiated accident victims (3,9,12). The entire 42-day clinical observation period was therefore used as the quantal-response time base for these two effects. No deaths occurred in any group between 42 and 60 days, so the time base in this instance can be extended to make this LD_{50} conform to the 60-day interval as is customarily used for man (3).

To illustrate the results of the line-fitting program, the probit analyses for anorexia in 2 days and death in 60 days are graphed in Figs. 3 and 4. The probit regression formulae are shown in Tables II and III along with the ED_{50} for these responses resulting from linear or log-dose transformation. The chi-square goodness-of-fits are shown and compared in Table IV. Some question may be raised about the adequacy of the fit of these data to the regression lines for all responses and dosage expressions. The 95% confidence intervals for the ED_{50} point of all of these probit regression lines are shown in Fig. 5.

Discussion

These results expressed as ED_{50} for radiation induced anorexia, nausea, vomiting, and diarrhea, and the LD_{50} for 60 days postirradiation death of man agree well with the majority of dose-response estimates derived

TABLE IB

Frequency of fatigue, diarrhea, and death in single radiation exposure of therapeutic and accident patients of ORINS Medical Division.

Mean Dose (Rad)	Total Cases	Fatigue Yes	Fatigue %	Diarrhea Yes	Diarrhea %	Death Yes	Death %
31.7	30	6	20	4	13	1	3
65.2	38	18	47	5	13	5	13
187.5	22	15	68	9	41	7	32
303.8	10	6	60	9	90	5	50

TABLE II

Probit analysis of effective doses for gastrointestinal and systemic clinical responses to total-body irradiation in man (using arithmetic dose).

Clinical Response	Equation P = a (dose) + b		$ED_{50} \pm$ S.E. (m)	
	Probit Units (a)	(b)	Epigastric Dose (Rads)	Midline Air Dose[a] (R)
Anorexia[b]	0.017	3.609	82 ± 32	124
Nausea[b]	0.008	3.837	138 ± 20	209
Vomiting[b]	0.008	3.588	173 ± 18	262
Fatigue[c]	0.004	4.428	136 ± 36	206
Diarrhea[c]	0.008	3.441	194 ± 19	294
Death[d]	0.006	3.347	281 ± 44	425

[a] As if all doses were from cesium-137 gamma rays, so 66 absorbed tissue rads = 100 R measured in air at theoretical midline without the patient present.

[b] Incidence of response through 2 days.

[c] Incidence of response through 42 days.

[d] Incidence of response through 60 days.

TABLE III

Probit analysis of effective doses for gastrointestinal and systemic clinical responses to total-body irradiation in man (using log-dose transformation).

Clinical Response	P = a (log dose) + b		$ED_{50} \pm$ S.E. (m)		
	Probit Units (a)	(b)	Epigastric Dose (Log_{10} Rads)	(Rads)	Midline Air Dose[a] (R)
Anorexia[b]	3.431	- 1.275	1.8291 ± 0.0837	68	101
Nausea[b]	2.301	+ 0.362	2.0152 ± 0.0640	104	157
Vomiting[b]	2.369	- 0.061	2.1360 ± 0.0640	137	201
Fatigue[c]	1.329	+ 2.360	1.9868 ± 0.1068	97	147
Diarrhea[c]	1.895	+ 0.712	2.2622 ± 0.0900	183	277
Death[d]	1.734	+ 0.665	2.4999 ± 0.1670	316	480

[a] As if all doses were from cesium-137 gamma rays, so 66 absorbed tissue rads = 100 R measured in air at theoretical midline without the patient present.

[b] Incidence of response through 2 days.

[c] Incidence of response through 42 days.

[d] Incidence of response through 60 days.

TABLE IV

Comparison of chi-square goodness-of-fit of probit equations using rad dose (Table II) with those using logarithmic rad dose (Table III).

Response	Dosage Expression: Rad Dose			Dosage Expression: Log-Rad Dose		
	X^2	%	"Conf"[a]	X^2	%	"Conf"
Anorexia	0.3965	84	75	1.2087	53	--
Nausea	3.7305	15	--	0.7888	65	81
Emesis	4.6525	9[b]	--	0.7888	65	84
Fatigue	5.8577	5[b]	--	2.3117	31	$\leq$ 75
Diarrhea	1.5316	46	80	6.0994	5[b]	--
Death	1.2043	53	--	0.2047	91	84

[a] "Conf" expresses the level of confidence in percent that a significant difference in goodness-of-fit exists between that obtained by rad dose and log-rad dose usage.

[b] Borderline acceptable fit.

Chi-square (X^2) calculated for 4-point probit fit, using 2 degrees of freedom.

in other studies and reviews (2,3,11,25-28). The 95% confidence limits about the regression lines indicate, however, that these numbers can be used only with prudent restrictions. Greater precision may be needed in clinical recording of symptoms and signs or in the objective digital encodement system used in this study. The failure, however, to obtain meaningful data about the incidence of listlessness or apathy, and of fatigue after radiation exposure would seem to reflect other difficulties. Since most hospital patients with advanced malignancies suffer from mental depressions and anxieties, listlessness, apathy, and fatigue might be expected to be so common that any increased incidence would be obscured or go unnoticed unless specific tests were made by the clinical staff to elicit quantitative rather than quantal responses. Observations among the Japanese casualties (10-12), the Y-12 and other accident cases (4-9), moreover, indicate that "fatigue" should be modified conceptually as a radiation response to be increased fatigability (3), since this effect is manifested best when work is attempted. Even so, the present study supports the view (3) that this effect may not be part of the prodromal syndrome, but a delayed symptom belonging more properly with the delayed symptoms of the acute radiation syndrome itself. Diarrhea, similarly, does not appear to be a symptom of the prodromal response per se. Its occurrence immediately after total-body exposure in the prodromal time period is a sign of massively supralethal radiation exposure and portends an early death from central nervous system, cardiovascular, and gastro-intestinal damage (3,29). The present study shows that an absorbed tissue dose of about 200 rads will cause half of those so exposed to develop diarrhea sometime later during the 6-week postirradiation period. The ED_{50} for this

response approaches the lethal range of radiation dosage. Whether the incidence of this symptom in this population has a statistical correlation with the observed deaths is being studied.

Besides agreeing with previous dosage approximation by others, these results also show an internal agreement that appears logical as well as intuitively fortunate as shown in Fig. 5. Clinically assumed severity of response varies in proportion with effective dosage. The choice of which set (Table II or Table III) of derived ED_{50}'s to use (rad versus log-rad) is made difficult by the failure of the statistical comparison of the goodness-of-fit data tabulated in Table IV, to support the almost universal contention that the biologic responses to radiation exposure are linearly rather than logarithmically distributed. This linear assumption is forced upon the clinician as well as the radiobiologist by the common observations that all animals including man have lower and upper thresholds of radiation dose-response. The impressively greater confidence levels in goodness-of-fits of the regression lines with log-dose usage would seem to imply that the data reported here are distributed better log-normally. Figures 6A and 6B show the distribution of sensitivities (probability densities) of these responses in relation to dose that result from the two different dosage usages. Illogically, no log-dose is too small to produce a given response and none large enough to effect 99% of the population until unacceptably large levels of radiation are reached (about 10,000 rads for the LD_{99}). This disagreement with practical knowledge is illustrated better by Figs. 7 and 8, which compare the distribution of two sensitivities that might be "expected" from the studies of others (derived from Langham, Brooks, and Grahn, Ref. 2) with

that "found" in this study using log-dose. The sensitivity to prodromal response has no lower threshold (Fig. 7) and that for death has no upper one (Fig. 8). In view of these discrepancies and the need for tolerance limits, linear dose relationships would seem preferable in spite of their poorer statistical support. The actual ED_{50}'s obtained by the two methods are not statistically significantly different as the overlapping 95% confidence limits illustrate in Fig. 5.

Figure 9 locates the LD_{50}'s obtained in this study in reference to the ranges (27,28) of lethal doses with which most observers would agree. The $LD_{50/60}$ is considered the best expression of the median lethal dose for the acute hematologic syndrome in man and, therefore, the number that might express best the radiobiologic relation of man to other animals in regard to relative radiosensitivity, and recovery rates from radiation damage. We must remember, however, that the present estimate of $LD_{50/60}$ for man of 281 $\pm$ 44 epigastric rads (425 $\pm$ 66 medial air dose in R) is based upon the incidence of death among 93 patients who because of their advanced malignant diseases had a high probability of dying in spite of radiotherapy rather than from it. This $LD_{50/60}$ is, therefore, heavily biased by an uncorrected incidence of nonradiologic death. That it is not significantly different from previous estimates is surprising (3). Since it would seem justified to assume that diseased populations would be sensitized to show increased responses in all categories of radiation induced effects, including death, these ED_{50}'s and LD_{50} might be considered the least doses required for these responses, and perhaps should be increased for normal adult man. The correction of such data derived from sick man to numbers that can be used

to predict the dose-response relationships of well man is not much more certain than the process of deriving the LD_{50} of man from that of the mouse. Statistical methods are, of course, available for correcting dose-response probabilities in the presence of a natural incidence of that response in the study population (30). The native incidence of the responses studied here without exposure (zero intercepts: Table II, column b; Figs. 3A,4A, and 6A) may be the best measure of initial error in the data caused by disease. Its use here as a correction factor is more complex than usual because the hematologic responses of some of these patients (to be reported) show that the total-body irradiation was therapeutically effective, and altered to an unknown extent the death-probability of some of the patients being treated. No dose correction factor for converting these ED_{50}'s from sick to well man is now available. Therefore, it is hoped that the incorporation in the future of the studies of others upon the effect of total-body irradiation upon nonhematologic diseases will enable such a correction to be made.

SUMMARY

The dose-response relationships for anorexia, nausea, vomiting, fatigue, diarrhea, and death were determined retrospectively without correction for natural incidence of these responses in 100 patients, 93 of whom suffered at the time from various blood dyscrasias. The ED_{50} for the least prodromal response, anorexia, was determined to be 82 $\pm$ 32 absorbed epigastric rads. The $LD_{50/60}$, uncorrected for nonradiologic deaths, was found to be 281 $\pm$ 44 absorbed rads as from a midline dose of 425 R.

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LEGENDS

Fig. 1 Scale model of cesium-137 total-body irradiation facility used in the radiotherapy of 87 of the 100 patients studied.

Fig. 2 Adult water phantom isodose curves of cesium-137 total-body irradiation facility showing (shaded area) relative volume and location of absorbed tissue dose (average epigastric rad) used as the common dosimetry unit in this study.

Fig. 3 Computer derived probability regression lines and 95% confidence intervals for the quantal postirradiation response, anorexia within 48 hours, in relation to linear (A) and logarithm (B) epigastric rads of total-body irradiation. The dotted line is the expected dose-response relationship according to other studies.

Fig. 4 Computer derived probability regression line and 95% confidence intervals for the quantal postirradiation response, death within 60 days, in relation to linear (A) and logarithmic (B) epigastric rads of total-body irradiation. No corrections for death from causes other than irradiation were made.

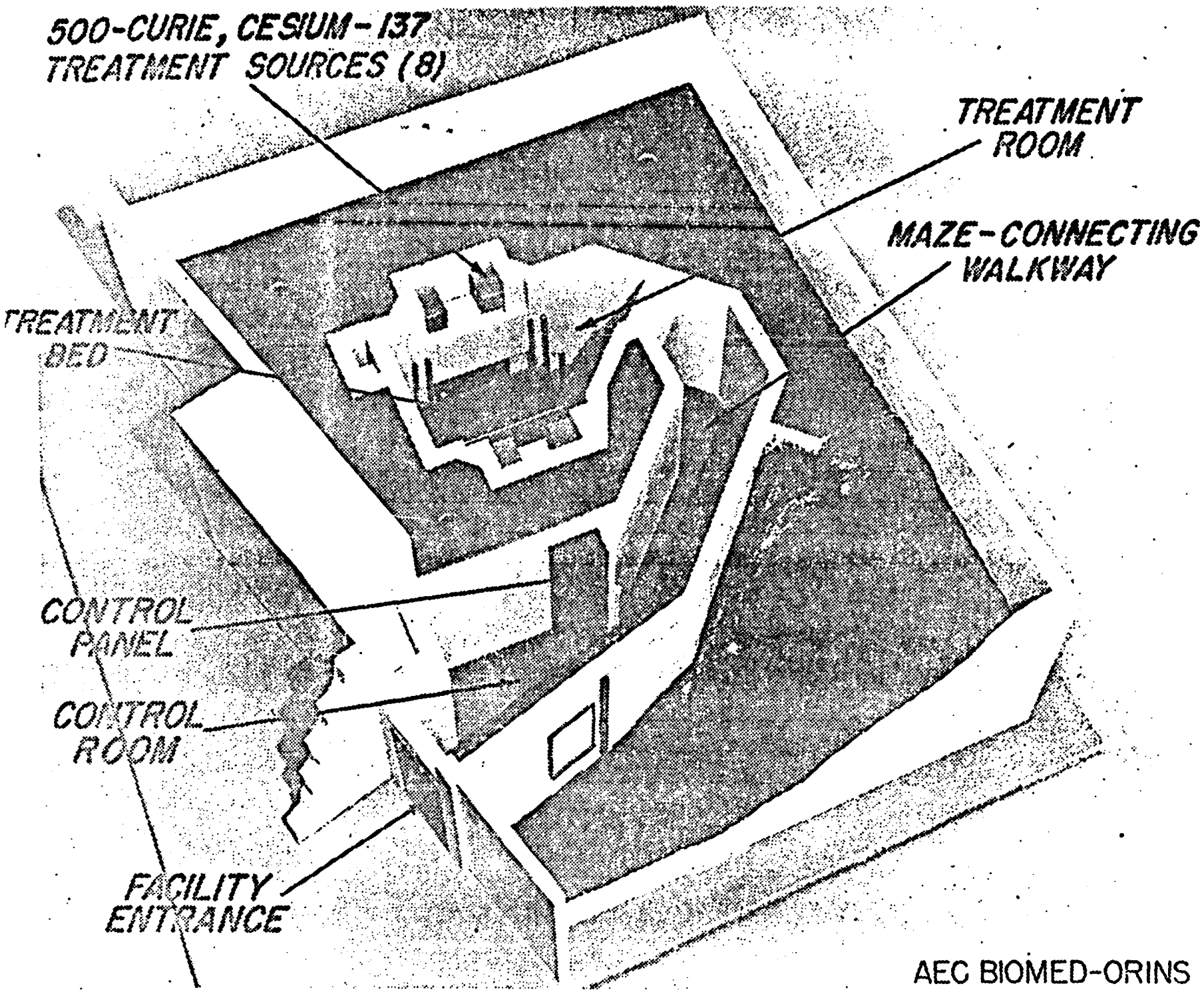
Fig. 5 Comparison of the ED_{50}'s and their respective 95% confidence limits derived from linear and logarithmic dose-probit analyses of percent incidence of anorexia, nausea, vomiting, diarrhea, and death in 100 hospital patients. The responses are arranged in order of increasing clinical severity assumed from the rank of the effective doses.

Fig. 6 Graph of the frequency distributions of population sensitivities (first derivatives of the probit regression equations) for anorexia, nausea, vomiting, diarrhea, and death in respect to change in linear rad dose (A) and logarithmic rad dose (B) of total-body irradiation.

Fig. 7 Graph comparing human sensitivity to prodromal syndrome "expected" from previous estimates with that derived from the response-dose relationship determined in this study.

Fig. 8 Graph comparing the human sensitivity to death within 60 days after radiation exposure "expected" from previous estimates with that derived from this dose-response relationship determined in this study.

Fig. 9 Graph comparing the linearly and logarithmicly derived LD_{50}'s for man obtained in this study with best estimates of the United Nations Scientific Committee on Effect of Atomic Radiation (27) and the National Academy of Science - National Research Council Committee on Biological Effects of Atomic Radiation (28) adapted from Langham, et al. (2).



AEC BIOMED-ORINS

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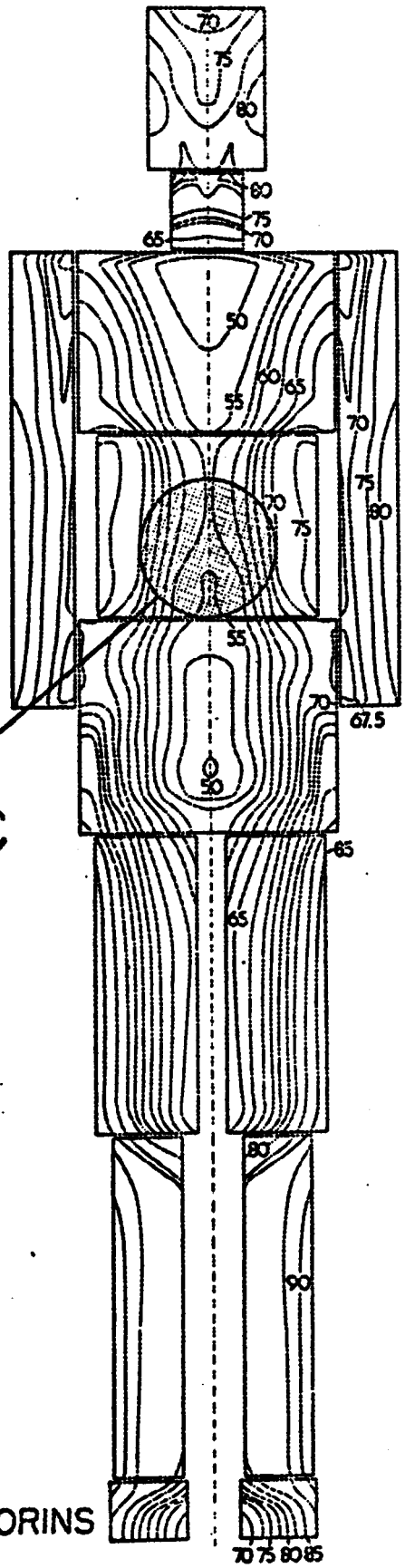

66 AVERAGE MIDEPIGASTRIC RADS

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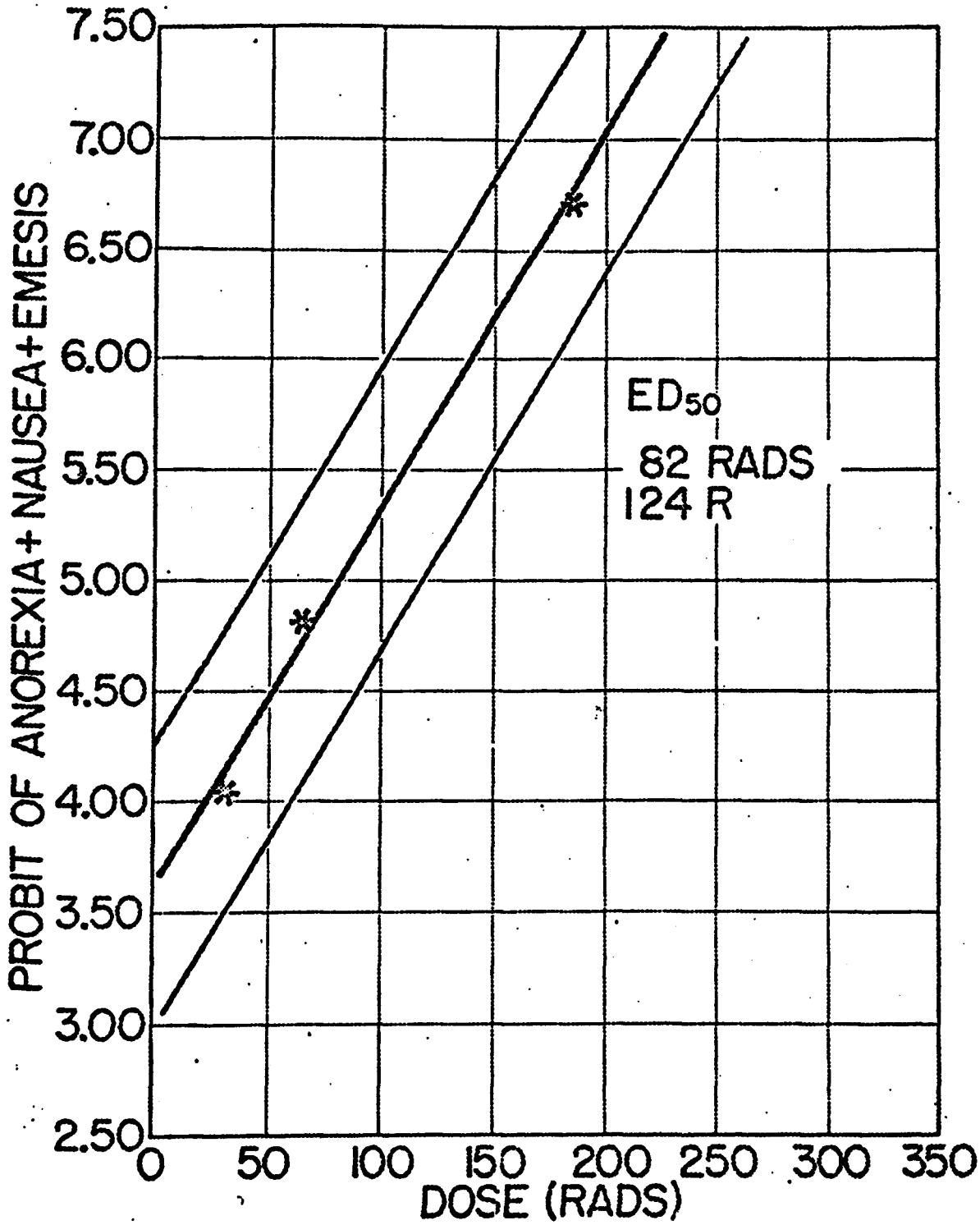

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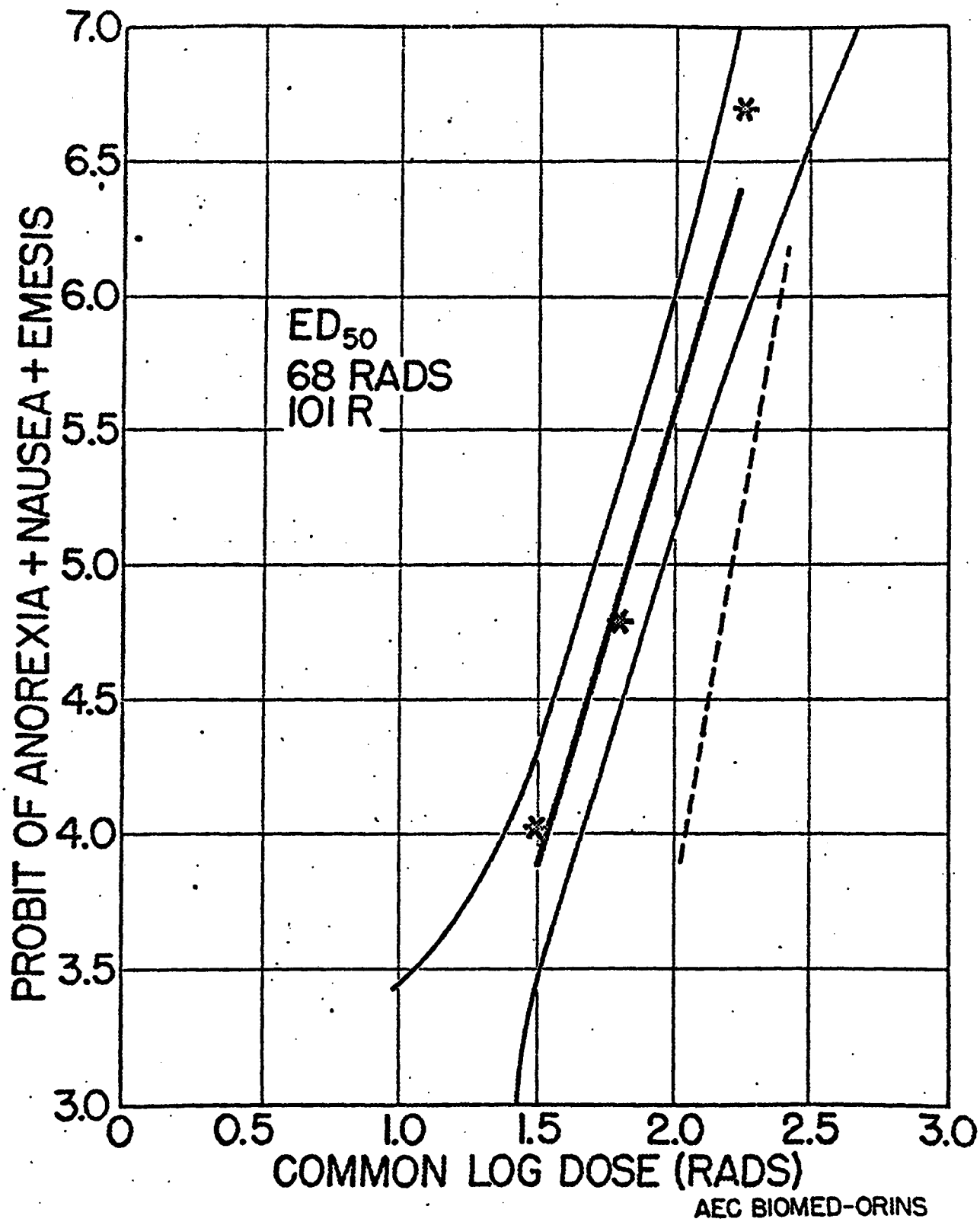
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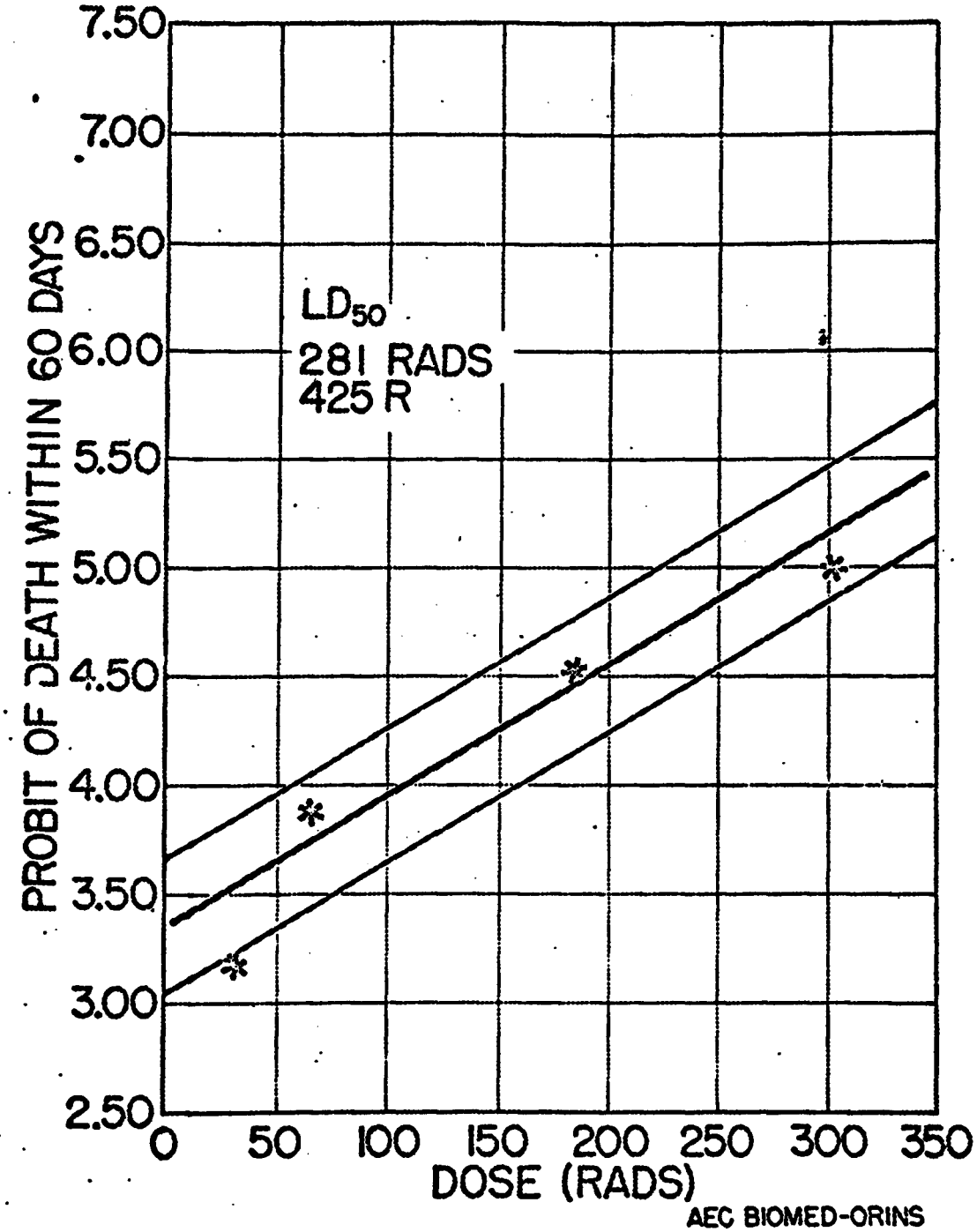
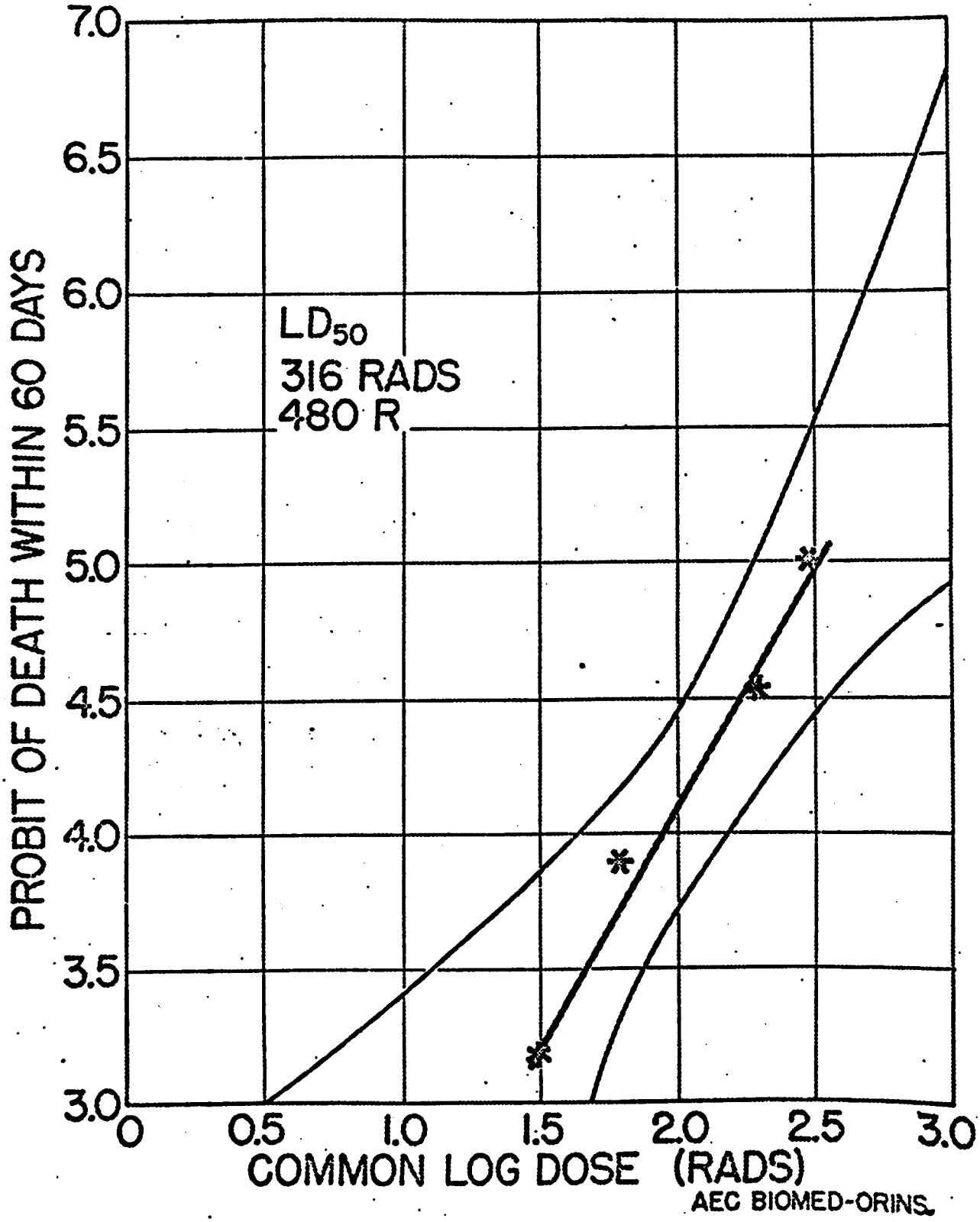
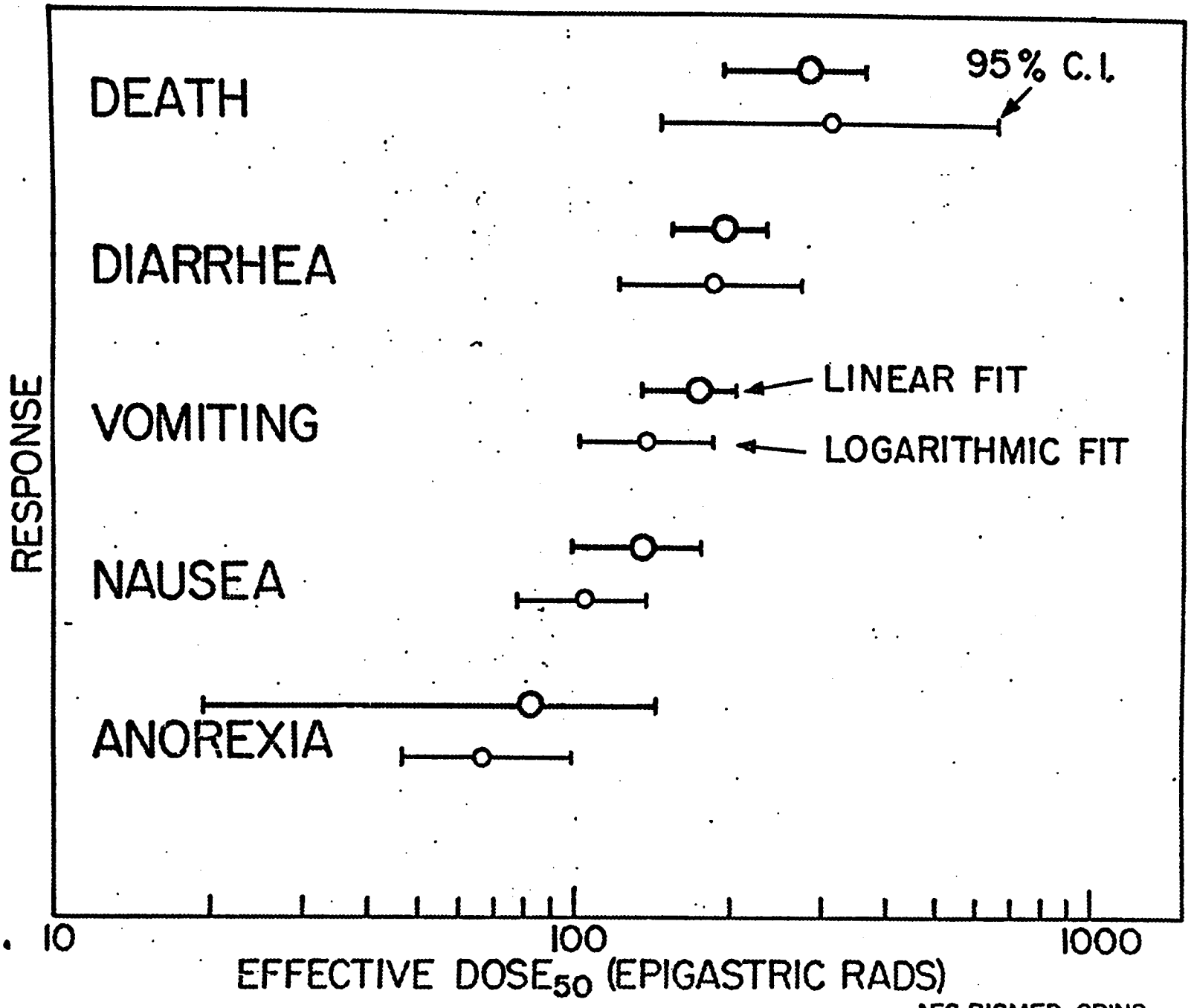
AEC BIOMED-ORINS


7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
PROBIT OF DEATH WITHIN 60 DAYS
LD50
281 RADS
425 R
0
50
100
150
200
250
300
350
DOSE (RADS)
AEC BIOMED-ORINS


7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
PROBIT OF DEATH WITHIN 60 DAYS
LD50
316 RADS
480 R
0
0.5
1.0
1.5
2.0
2.5
3.0
COMMON LOG DOSE (RADS)
AEC BIOMED-ORINS.



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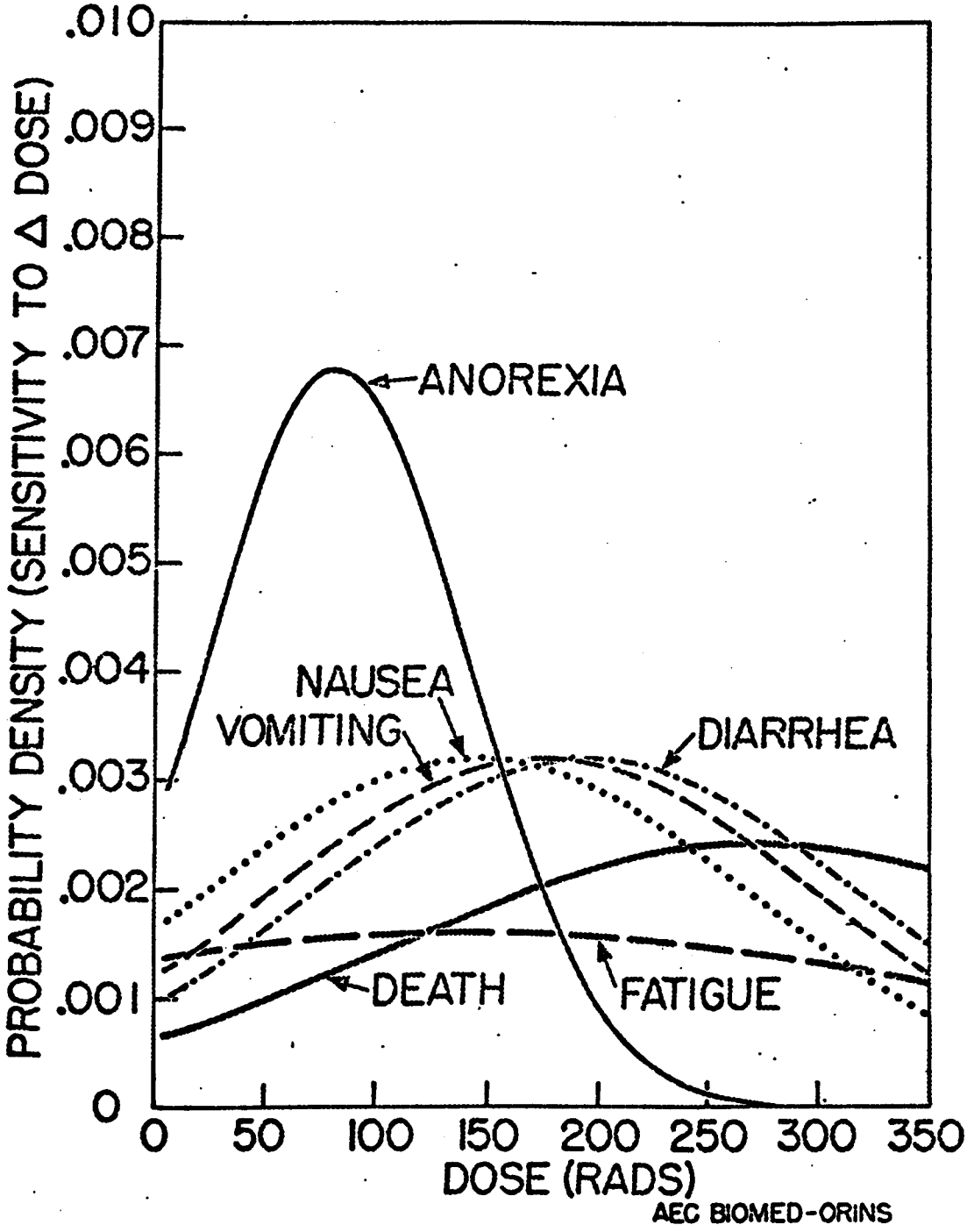
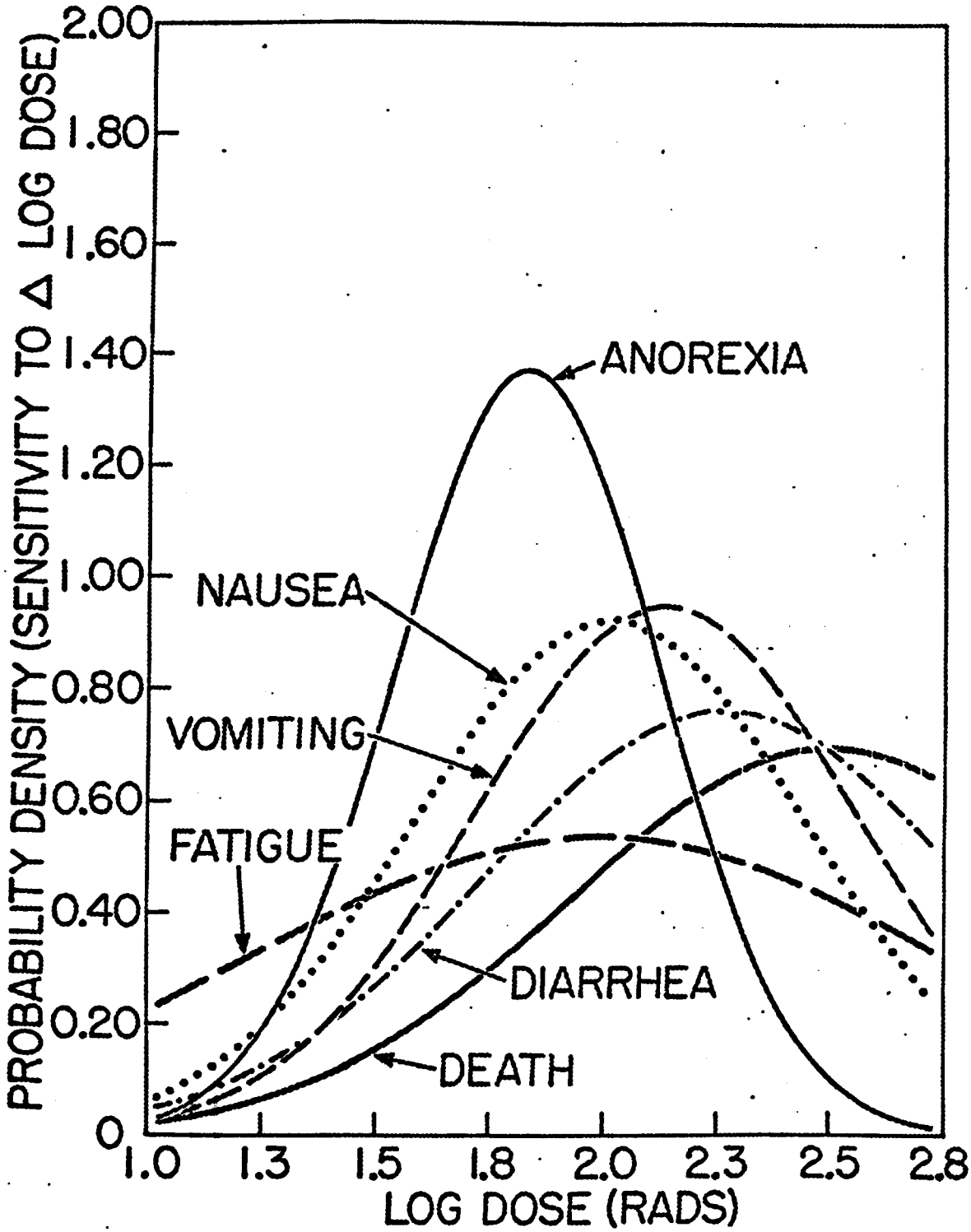
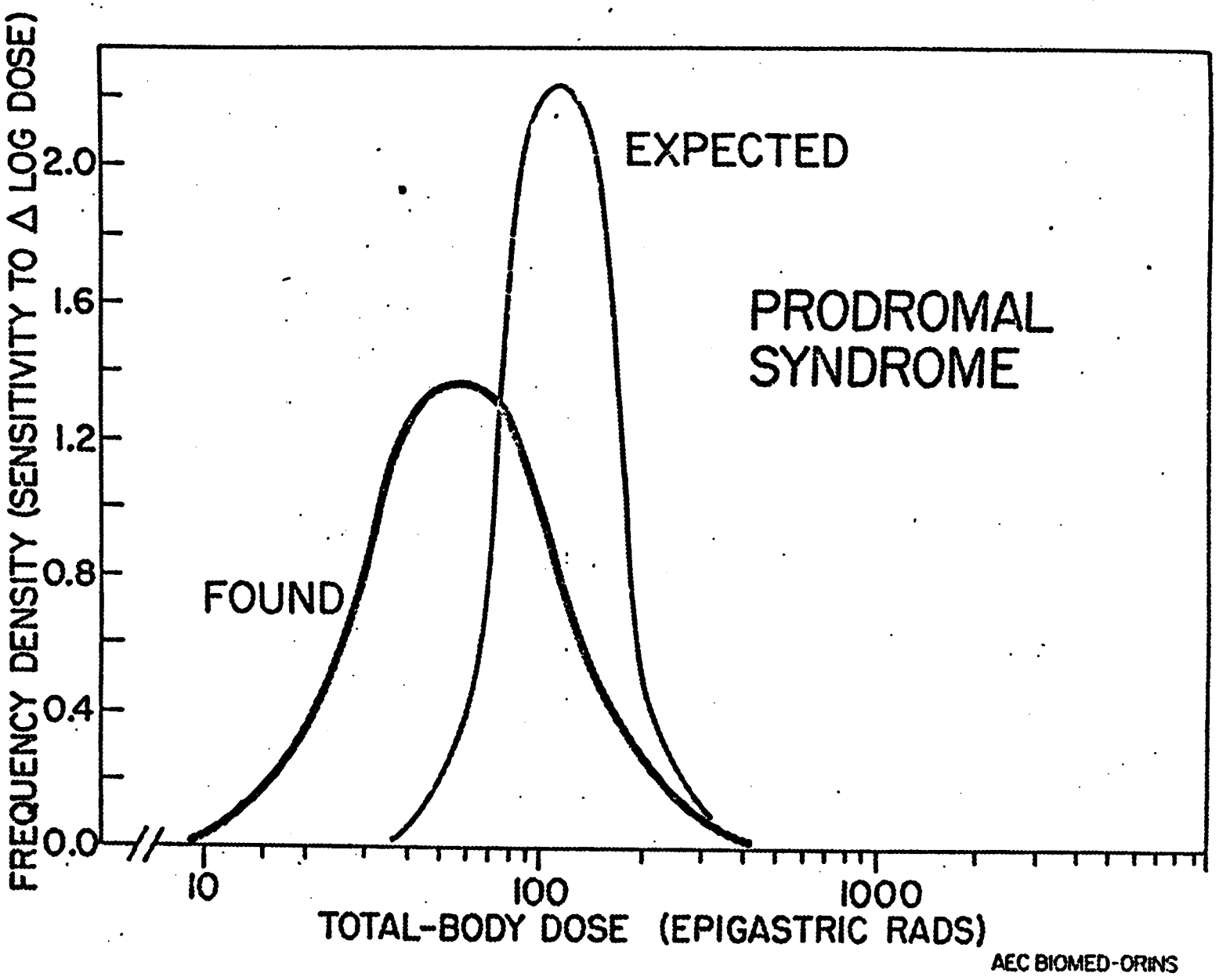
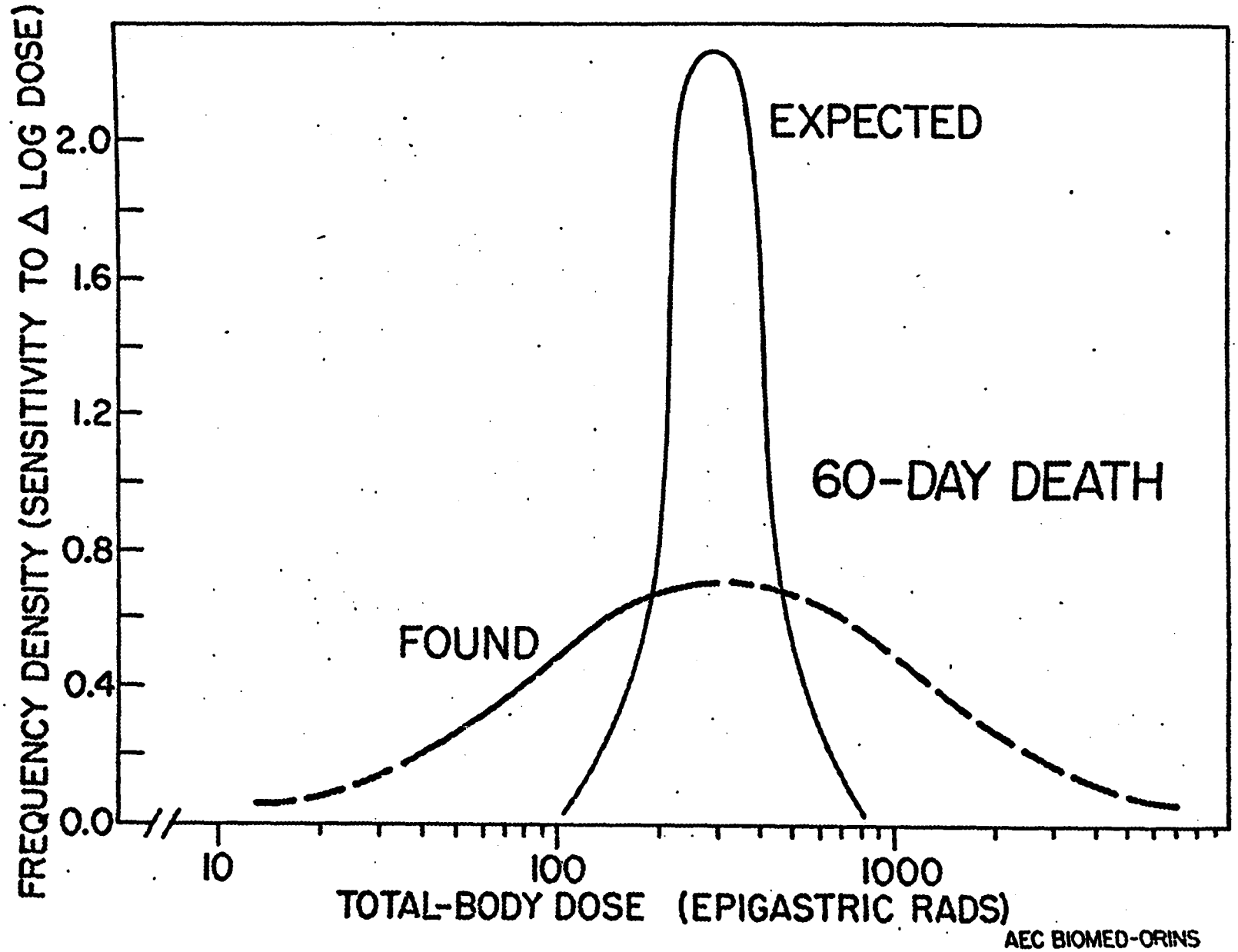
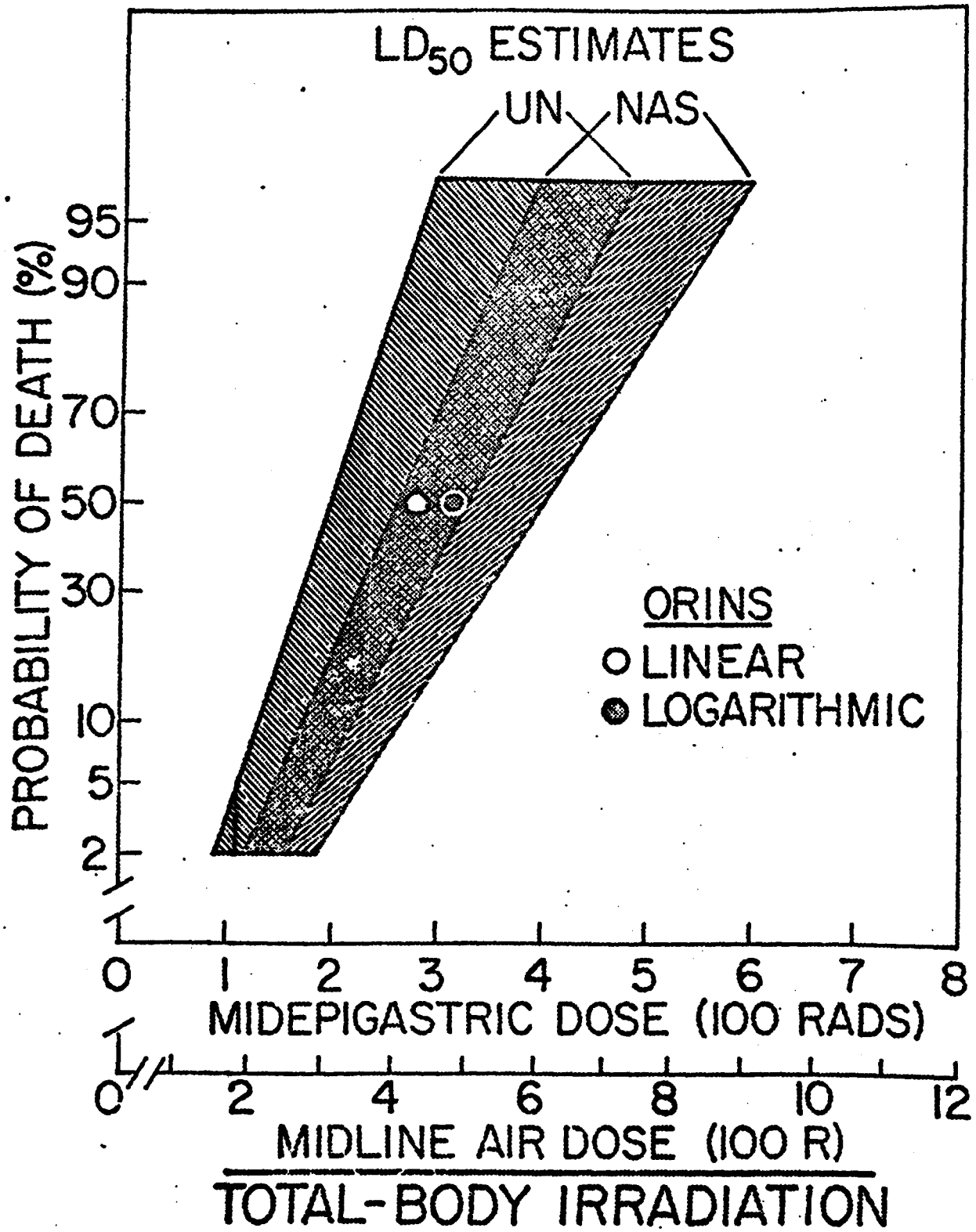

PROBABILITY DENSITY (SENSITIVITY TO Δ DOSE)
.010
.009
.008
.007
.006
.005
.004
.003
.002
.001
0
ANOREXIA
NAUSEA
VOMITING
DIARRHEA
DEATH
FATIGUE
0
50
100
150
200
250
300
350
DOSE (RADS)
AEC BIOMED-ORINS



AEC BIOMED-ORINS


FREQUENCY DENSITY (SENSITIVITY TO Δ LOG DOSE)
2.0
1.6
1.2
0.8
0.4
0.0
EXPECTED
PRODROMAL
SYNDROME
FOUND
10
100
1000
TOTAL-BODY DOSE (EPIGASTRIC RADS)
AEC BIOMED-ORINS


FREQUENCY DENSITY (SENSITIVITY TO Δ LOG DOSE)
2.0
1.6
1.2
0.8
0.4
0.0
EXPECTED
60-DAY DEATH
FOUND
10
100
1000
TOTAL-BODY DOSE (EPIGASTRIC RADS)
AEC BIOMED-ORINS



TOTAL-BODY IRRADIATION

AEC BIOMED-ORINS