Relationship Between Radiation Dosage and Biological Response (Radiation Dosage and Mortality Rate)

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照射線量と生物学的反応との相関々係について (照射線量と死亡率)

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近年多数の近交系動物が医学の研究にとつて貴重な資料であることが明らかになつたばかりでなく，色々の研究に適した系統の育成が可能となつて来た．併し，最近かゝる近交系動物の系統，性の相違に基づく実験結果の相違が問題となつて来た．かゝる相違について近来色々の反省と吟味が加えられ動物実験の精度を増す努力が行われている．今回4系統のマウスにX線及び ^{60}Co γ線全身一時照射を行い，照射線量と死亡率との相関々係について検討を加えた．
使用動物は S.M 系，d.d.N 系ＣＦ１系，CFw 系マウス，合計 750匹照射時年令40～42日，X線 ^{60}Co γ 線全身一回照射後30日間観察死亡率（%）の Probit Y と照射線量の対数（X）との間には直線関係があり（表2，5），死亡率30～60%の範囲内では（表7）に示す様にX線照射群では36～18γ Co^{60} γ線群では11～15γという小さい線量で，死亡率を10%上昇させる．従つて死亡率を対象とした動物実験の効果の判定には厳めて厳重な線量測定が必要である事を示している．又死亡率30～60%の間で10%死亡率上昇に必要とする線量を 1.0と仮定し，他の死亡率範囲内での10%，死亡率上昇に必要とする線量との比を見ると，X線 ^{60}Co γ線照射群及び本実験の4系統以外の他の系との間にも略々同様の線量比を見た．

I. Preface

It may be safely said that the validity of achievements of medical research are proportionate to the accuracy of animal experiments. Recently, it has not only been realized that many inbred strains of animals are valuable material in medical research but also it has become possible to breed strains suitable for the various studies. However the difference in results of experiments due to different strains and sex has become a problem, and it has become necessary in recent years to reconsider such matters and carry out further study to increase the accuracy of animal experiments. Because of its importance in research work in the fields of medicine and biology, "the Research on the Physiological Charateristcs of Various Types fo Mice" is being carried out by a research group financed with scientific research funds of the Education Ministry. As one phase of this study, I had been previously carrying out work on whether or not there are any differences in the sensitivity to radiation [1)2)3)4)5)6)7)8)] by strain or sex of animals using four strains of inbred mice (SM strain, ddN strain, CF #1 strain, CFW strain). [9)10)11)12)13)14)] In the present study, a study has been done on the relationship between the radiation dosage and biological response along with an attempt at a review of documents so as to establish a basis for future animal experiments using radiation.

II. Method of Research

1) Death as a biological response

John B. Storer, [8)24)] Payne S. Harris, John E. Farchner, Wright H. Langham have demonstrated that there is a quantitative relationship between mortality rate and radiation dose. When the death rate (%) of mice exposed to radiation is converted into Y (probit), the relation with dose X is as follows:

$Y = a + b \log X$

2) Animals used (Table 1)

	Sex	Control	CF #1	CFW	SM	ddN
Group exposed to Co^{60} gamma rays	F	27	36	36	49	47
	M	28	36	36	45	45
Group exposed to X-rays	F	31			81	77
	M	32			72	72
Total	750					

Age at time of exposure 40–42 days

The mice were fed only CE-2 solid feed and allowed to drink water from a drinking bottle at liberty.

4 to 5 mice were kept in one 18×16×20 cm wire cage.

The mice were all purchased from the Experimental Animal Central Research Laboratory.

3) Method of irradiation

a) Method of X-ray irradiation [9)11)12)]

A round card-board irradiation box (2 mm thick, 2.5 cm high, 20 cm diameter) with 12 partitions was fixed on the center of the top of a 110 cm high, 60×60 cm rack made of wooden boards 2 cm thick and 5 cm wide. An ionization chamber of Siemens Universal Dose meter is inserted into one partition. 10 to 11 mice were exposed at one time and the exposure dosage was determined with a integrating meter.

Exposure conditions

Apparatus Toshiba KXC-18 model 200 KVP 25 mA

Filter 1.0mm Cu+0.5mm Al half value layer 1.73 Cu mm

Dose rate 62r/min : Focus substance distance 50 cm

Exposed doses 400 r 600 r 800 r (air dose)

b) Method of Co^{60} gamma exposure

Exposure was carried out after putting eight mice each in cardboard irradiation boxes of 2mm thickness, 2cm high and 14×8cm in width and length. (The variation in dosage distribution in an exposure field of 14×8cm is less than ± 0.5%).

Apparatus Toshiba 107 model Co^{60} large dose remote irradiation apparatus

Source-animal distanece 50cm, dose rate 66r/min

Exposure does 500 r 600 r 700 r 800 r

III. Results and Considerations

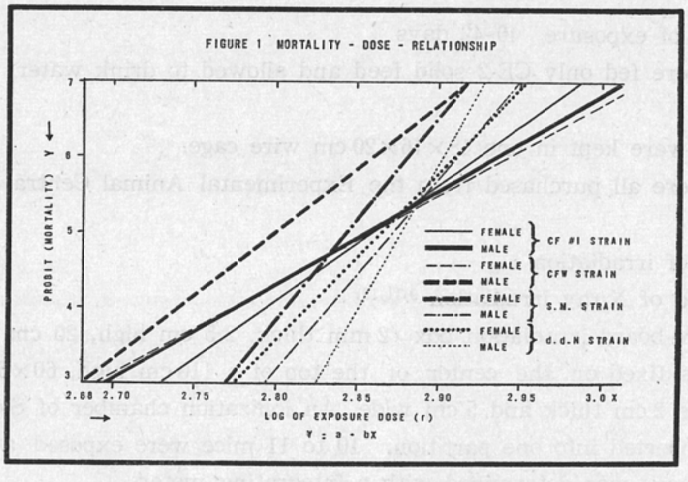
(1) Co^{60} gamma ray exposure group

(a) Equation for mortality rate and dose

(Table 2) The equation between probit Y of mortality rate (%) and logarithm, X-for radiation dose and the LD 50/30 value obtained from this equation are as follows:

Strain	Sex	Dose-Mortality-Relationship	LD50/30±SE (log)
CF#1	F	Y=4.993 +15.439 (X−2.8545)	2.8549±0.0162
CF#1	M	Y=4.985 +12.375 (X−2.8608)	2.8537±0.0196
CFW	F	Y=5.1468+12.07 (X−2.8703)	2.8578±0.0191
CFW	M	Y=5.544 +16.941 (X−2.8331)	2.8010±0.0173
S.M	F	Y=5.651 +27.042 (X−2.8714)	2.8475±0.063
S.M	M	Y=4.8539+26.07 (X−2.8668)	2.8724±0.0156
ddN	F	Y=5.0214+22.447 (X−2.8651)	2.8641±0.0021
ddN	M	Y=4.6337+38.95 (X−2.8673)	2.8767±0.0018

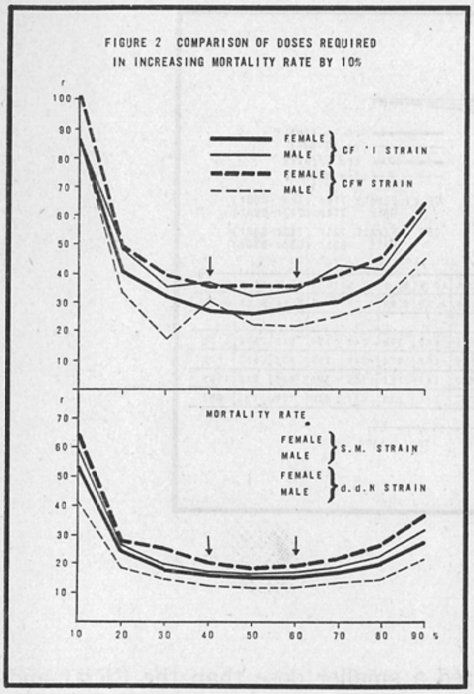
Figure. 1



These results may be expressed in linear form as shown in Figure 1.

Male and female of SM strain, male of CF#1 strain and female of CFW strain demonstrated an almost identical gradient, but the others showed obviously different gradients. The gradient b obtained from Table 2 and Figure 1 is in the following order :

Figure. 2



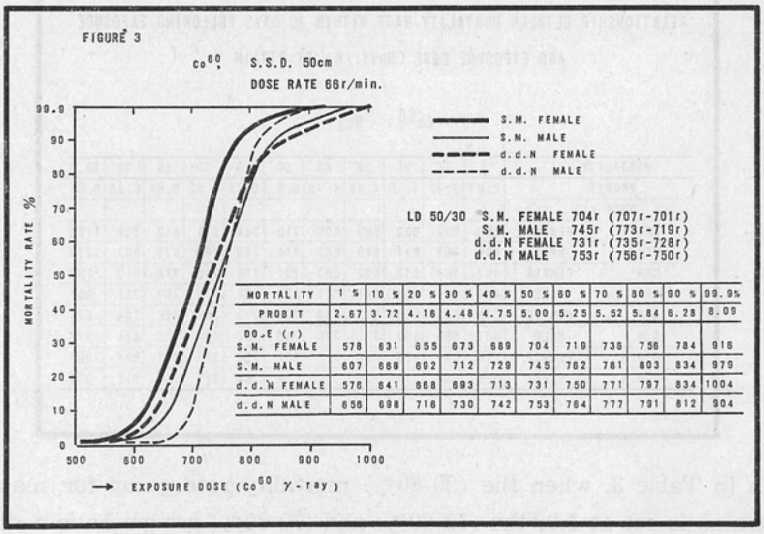
ddN♂>SM♀>SM♂>ddN♀>CFW♂>CF#1♀>CFW♂>CFW♀

There was no definite difference by strain between male and female. The SM and ddN strains definitely demonstrated a greater gradient than the CF#1 and CFW strains. Also when $Y=a+bx$, a has a definitely large value. Therefore, the dosage must be accurately measured in exposure experiments with SM and ddN strains and care must be exercised in evaluating the experiment results when the mortality rate is the subject of study.

Figure 2 shows comparisons of dosages required to increase the mortality rate by 10% each for the four strains used in this experiment. Within the mortality rates of 30 to 60% for both sexes of all strains, the dosage required to increase this rate by 10% was approximately the same. This indicates that the sigmoid curve of the relation between the mortality rate (%) and dosage (r) in figures 3 and 4 is close to a linear relationship for mortality rates between 30 to 60%. As evident in figure 2 within the mortality rate of 30 to 60% the dosages required to increase the mortality rates by 10% are as follows:

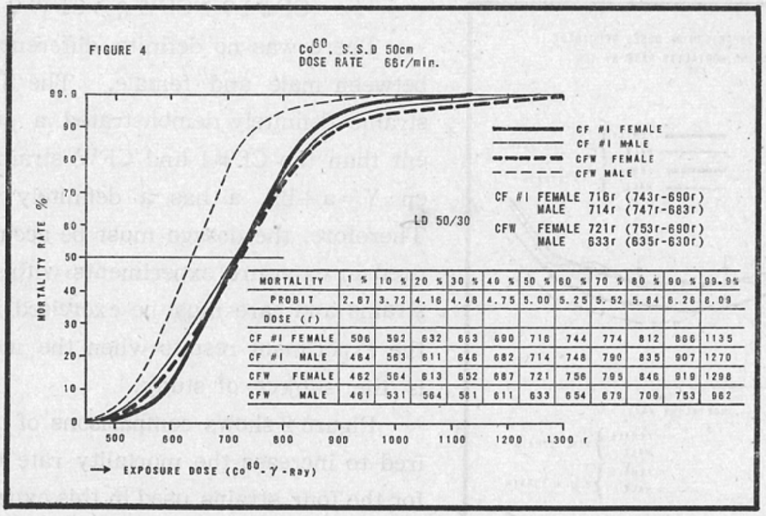
CFW strain　　F : 18 r　　M : 11 r

Figure. 3



MORTALITY	1 %	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	99.9%
PROBIT	2.67	3.72	4.16	4.48	4.75	5.00	5.25	5.52	5.84	6.28	8.09
DOSE (r) S.M. FEMALE	578	631	655	673	689	704	719	736	756	784	916
S.M. MALE	607	668	692	712	729	745	762	781	803	834	979
d.d.N FEMALE	576	641	668	693	713	731	750	771	797	834	1004
d.d.N MALE	656	698	716	730	742	753	764	777	791	812	904

Figure. 4



SM strain	F 15 r	M 16 r
CF#1 strain	F 26 r	M 33 r
ddN strain	F 18 r	M 11 r

In other words, the SM and ddN strains required a smaller dose than the CF#1 and CFW strain. This indicates the relation with gradient b as stated above. Thus, it is noteworthy that the mortality rate varies by 10% with a dosage of about 20 r (about 1/35 of LD50/30, exposure time about 20 seconds). The above relationship is summarized in Table 3.

Table. 3

RELATIONSHIP BETWEEN MORTALITY RATE WITHIN 30 DAYS FOLLOWING EXPOSURE AND EXPOSURE DOSE (Unit: rR) BY STRAIN

Co^{60} γ- Ray

MORTALITY (%)		1	10	20	30	40	50	60	70	80	90	99.9
PROBIT		2.67	3.72	4.16	4.48	4.75	5.0	5.25	7.52	5.84	6.28	8.09
DOSE (r)												
CF #I	FEMALE	506	592	632	663	690	716	744	774	812	866	1135
CF #I	MALE	464	563	611	646	682	714	748	790	835	907	1270
CFW	FEMALE	462	564	613	652	687	721	756	795	846	919	1298
CFW	MALE	461	531	564	581	611	633	654	679	709	753	962
S.M.	FEMALE	578	631	655	673	689	704	719	736	756	784	916
S.M.	MALE	607	666	692	712	729	745	762	781	803	834	979
d.d.N	FEMALE	576	641	668	693	713	731	750	771	797	834	1004
d.d.N	MALE	656	698	716	730	742	753	764	777	791	812	904

As shown in Table 3, when the (30-60%) mortality rate group for male and female for all four strains is set at 1.0, the (10-20%) and (70-80%) groups have a dose rate of 1.5

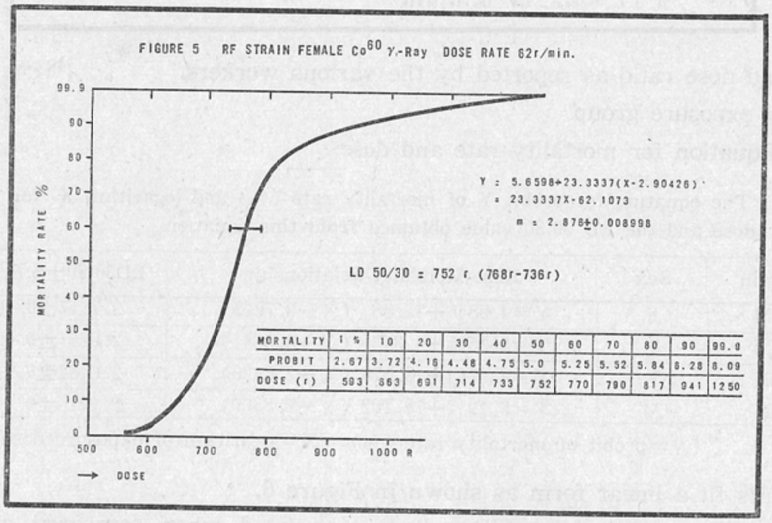
(Table 3) Relationship between mortality rate within 30 days following exposure for all strains and dosage (unit for values in Table-r)

Mortality	1—10%	10—20%	30—60%	70—80%	80—90%	90—99.9%	
Dose ratio	3	1.5	1.0	1.5	2.0	CF#1	10
						CFW	20
						SM F	16
						SM M	9
						ddN F	10
						ddN M	8

times; the (80-90%) group has a rate of 2.0 times and the(1-10%)group has a rate of 3.0 times. Furthermore, the (90-99.9%) group hae rates of 10.0 for the CF#1 strain; 20.0 for the CFW strain; 16.0 for female and 9.0 for male SM strain; 10.0 for female and 8.0 for male ddN strain. In other words, the dosage required for the same increase of 10% in mortality rate varies greatly from 1.5-2.0-3.0-10-20 times according to groups. Therefore, in evaluating the effects in exposure experiments to seek mortality rates, it is desirable to fix the range of mortality rate and carry out strict measurements of exposure dosages.

According to A.C. Upton, et al.[25] Y=5.6598+23.33 (X-2.904) for female RF strain mice as shown in Figure 5. Gradient b resembles that of female ddN strain mice (22.447)

Figure. 5



and the LD50/30 value is 752 r. The dose rate required to increase the mortality rate by 10% for this strain was the same as for the four strains used in this experiment, but in the (80-90%) groupe the high value of 6.0 times was obtained. J.B. Storer, et al.[26] carried out Co^{60} gamma ray exposure with a different dose ratio and obtained the equation of Y=5.183+17.801 (X-2.896) dose ratio 42 r/min with female CF#1 strain mice. The gradient b was larger than that of 15.439 for female CF#1 strain mice in this experiment, but the dose rate was 66r/min. According to J.B. Storer et al., the gradient b shows a tendency of being greater as the dose ratio increases. The LD50/30 value is 772 r and in this experiment it is 716 r. The difference is believed to be due to the difference in age of the animals, dose ratio at time of exposure, physiological and physical cinditions including raising environments. Table 4 shows the LD50/30 values, age of animals, number

Table. 4

COMPARISON OF LD 50/30 VALUE (^{60}Co-γ-Ray)

STRAIN	SEX	NUMBER OF ANIMALS	AGE	LD 50/30	RANGE	DOSE - RATE	CONFER
S.M	FEMALE	49	40 - 42	704 r	711 - 700	66r/min.	1
S.M	MALE	45	40 - 42	745 r	773 - 719	66r/min.	1
d.d.N	FEMALE	47	40 - 42	731 r	735 - 728	66r/min.	1
d.d.N	MALE	45	40 - 42	753 r	756 - 750	66r/min.	1
C.F.W	FEMALE	36	40 - 42	721 r	753 - 690	66r/min.	1
C.F.W	MALE	36	40 - 42	633 r	635 - 630	66r/min.	1
C.F.#I	FEMALE	36	40 - 42	716 r	743 - 690	66r/min.	1
C.F.#I	MALE	36	40 - 42	714 r	749 - 683	66r/min.	1
R.F	FEMALE	120	63 - 84	752 r	768 - 736	7.8r/min.	2
C.F.#I	FEMALE			720 r		62r/min.	3
C.F.#I	FEMALE	254	42 - 70	772 r	754 - 791	42r/min.	4
C.F.#I	FEMALE	80	42 - 70	785 r	738 - 814	15r/min.	4
C.F.#I	FEMALE	140	42 - 70	800 r	760 - 841	4r/min.	4
C.F.#I	FEMALE	120	42 - 70	1010 r	956 - 1084	1.5r/min.	4
C.F.#I	FEMALE	96	42 - 70	1081 r	985 - 1415	0.4r/min.	4
C.F.#I	FEMALE	100	42 - 70	1658 r	1325 - 2020	0.1r/min.	4
C.F.#I	FEMALE	60	42 - 70	2756 r		0.08r/min.	4

CONFER: 1. Miyagawa & Watanabe 2. A.C. Upton 3. J.B. Storer
4. J.F. Thomson, W.W. Tourtellotte

of animals and dose ratio as reported by the various workers.

(2) x-ray exposure group

(a) Equation for mortality rate and dose

(Table 5) The equation for probit Y of mortality rate (%) and logarithm X for radiation dose and the LD 50/30 value obtained from this equation

Strain	Sex	Dose-Mortality-Relationship	LD50/30±S.E. (log)
S.M	F	$Y=4.9855+12.38\ (X-2.7205)$	2.7217±0.0035
S.M	M	$Y=5.2505+4.313\ (X-2.6841)$	2.626 ±0.0039
ddN	F	$Y=4.9264+13.575\ (X-2.6429)$	2.6482±0.0181
ddN	M	$Y=5.1917+10.102\ (X-2.6809)$	2.661 ±0.0195

(Y=probit of mortality rate (%) X=logarithm of exposure dose)

The results fit a linear form as shown in Figure 6.

No systematic response by strain and sex was noted when compared with the Co^{60} gamma exposure group.

The range for LD50/30 values were log 2.80-(2.848-2.866) for the Co^{60} gamma ray exposure group and log (2.625-2.72) for the X−ray group. Thus, the X−ray group had a much wider range (the dispersion of the LD50/30 value was greater). The gradient b was in the order of ddN♀>SM♀>ddN♂>SM♂, and was much lower than the Co^{60} gamma ray exposure group. The difference by sex was greater in the SM strain than the ddN strain. That is, in the exposure experiment where the mortality rate is the subject of study, more strict measurement of dosage is necessary in the X-ray group as

Figure. 6

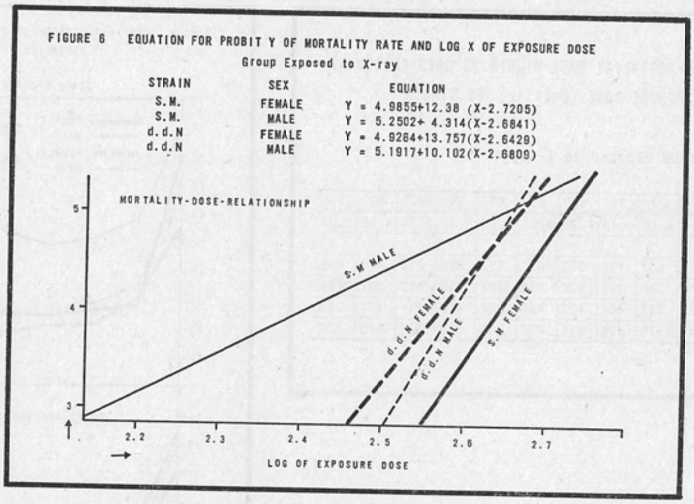
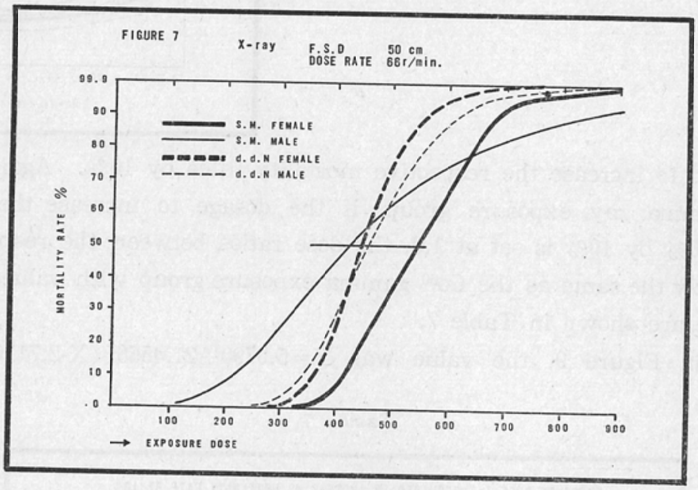


Figure. 7



compared with the Co^{60} gamma ray group. Table 6 shows the relationship between the mortality rate of all strains within 30 days following exposure and the exposure dose. Sigmoid curves as shown in Figure 7 were obtained from the mortality rate (%) and dosage (r). That is, the sensitivity was high among males up to 590 r (mortality rate of 70%) in the SM strain and up to 410 r (mortality rate 30%) in the ddN strain, and it was found that the difference in sensitivity by sex varied according to dose of exposure. Furthermore, as in the case of the Co^{60} gamma ray exposure group, within the mortality rate of 30 to 60%, the results were more or less linear and the dosage required to increase the mortality rate by 10% obtained by the same method as that for Co^{60} gamma ray exposure group was SM female (25 r), male (54 r); ddN female (19 r), male (26 r). Thus, it is evident that a far greater dose is required. Figure 8 shows the comparison of

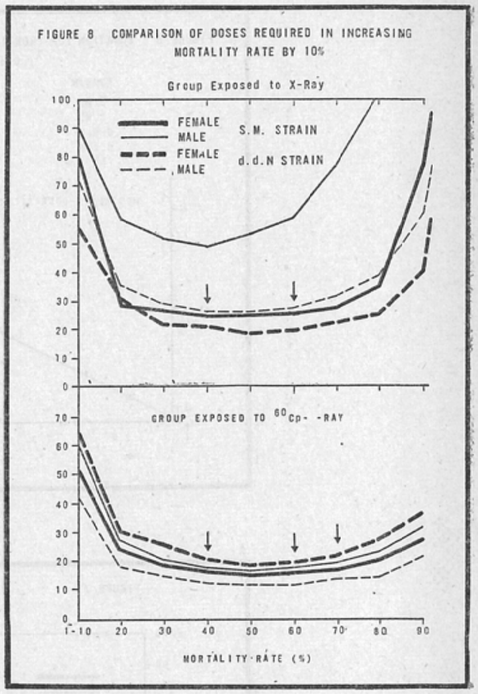
Table. 6

RELATIONSHIP BETWEEN MORTALITY RATE WITHIN 30 DAYS FOLLOWING EXPOSURE AND EXPOSURE DOSE (Unit: r) BY STRAIN

Group exposed to X-ray

MORTALITY (%)	1	10	20	30	40	50	60	70	80	90	99.9
PROBIT	2.67	3.72	4.16	4.48	4.75	5.0	5.25	5.52	5.84	6.28	8.09
DOSE (r)											
S.M. FEMALE	342	423	451	478	503	527	552	580	615	669	936
S.M. MALE	122	212	270	321	370	423	482	558	662	837	2100
d.d.N FEMALE	301	357	387	408	427	445	464	486	511	551	746
d.d.N MALE	270	343	379	408	434	459	486	517	556	615	929

Figure. 8



dosages required to increase the respective mortality rates by 10%. Again, as in the case of the Co^{60} gamma ray exposure group, if the dosage to increase the mortality rates between 30 to 60% by 10% is set at 1.0, the dose ratios between the respective mortality rates were exactly the same as the Co^{60} gamma exposure group with values of 3.0, 1.5, 1.0 and 2.0. These are shown in Table 7.

As shown in Figure 9, the value was Y=5.0790+21.4556 (X-2.7110) for RF strain

Table. 7

EXPOSURE DOSE (r) REQUIRED IN INCREASING MORTALITY RATE BY 10% IN THE 30-60% MORTALITY RANGE

		X-RAY		^{60}Co-γ-RAY	X-R/^{60}Co
S. M.	Female	25 r	>	15 r	1.7
S. M.	Male	36 r	>	16 r	3.5
d.d.N	Female	18 r	=	18 r	1.0
d.d.N	Male	26 r	>	11 r	2.4

		% 1-10	% 10-20	% 30-70	% 70-80	% 80-90	% 90-99.9
DOSE RATIO	^{60}Co	3	1.5	1.0	1.5	2.0	S.M. Female 16.0 S.M. Male 9.0 d.d.N Female 10.0 d.d.N Male 8.0
	X-RAY	3	1.5	1.0	1.5	2.0	S.M. Female 11.0 S.M. Male 23.0 d.d.N Female 11.0 d.d.N Male 12.0

Figure. 9

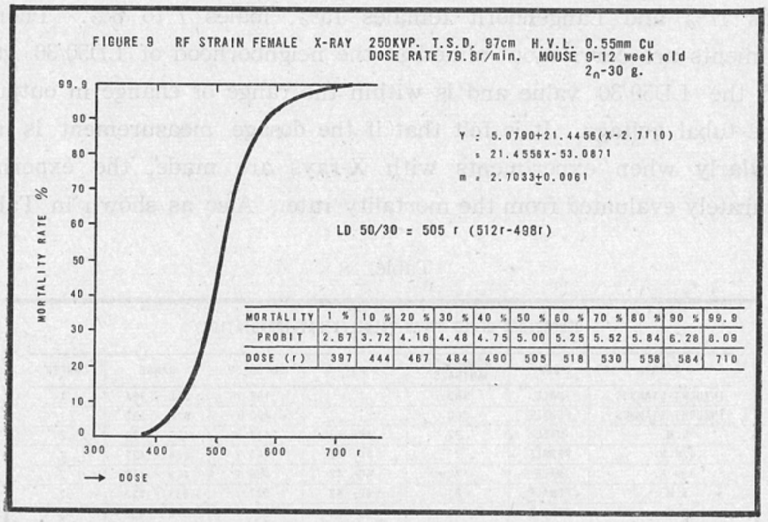
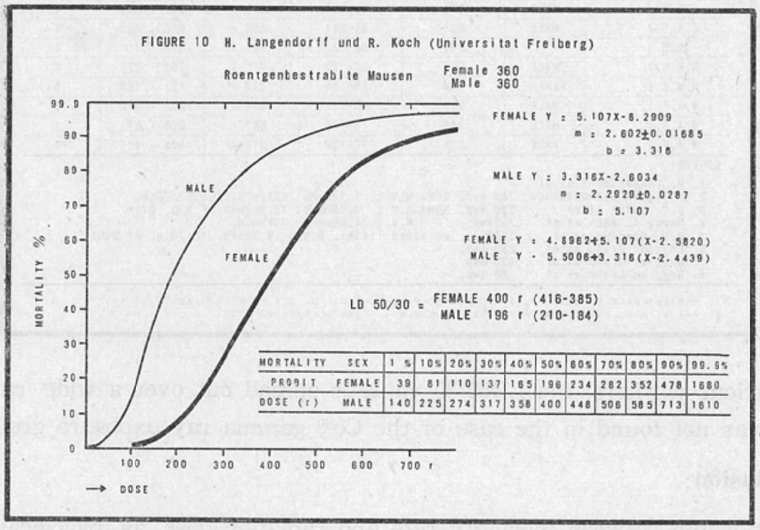


Figure. 10



female used by A.C. Upton, et al. and the gradient b was much greater than that for the SM and ddN strains. Furthermore, H. Langendorff, et al. obtained the following values with inbred mice as shown in Figure 10.

Female $Y=4.8962+5.107\ (X-2.5820)$

Male $\quad Y=5.5006+3.316\ (X-2.4439)$

Gradient b was low and had a value close to that of $b=4.31$ for SM female strain. In the RF strain, the dose required to increase the mortality rate by 10% for the mortality rates between 40 to 60% was 15 r. According to H. Langendorff, females required 45 r and males 35 r. On the contrary, the following changes in mortality rates took place at

25 r; for SM strain females 10%, males 5%; ddN strain females 7.6%, males 10%; RF strain females 17% and Langendorff females 15%, males 7 to 8%. Therefore, when animal experiments are carried out aimed at the neighborhood of LD50/30 value, 25 r is about 5% of the LD50/30 value and is within the range of change in output caused by changes in the tubal voltage. It is felt that if the dosage measurement is not carefully taken, particularly when experiments with X-rays are made, the experiment results cannot be accurately evaluated from the mortality rate. Also as shown in Table 8, according to the various workers, the LD50/30 value is spread out over a wide rang of 200 to 700 r which was not found in the case of the Co^{60} gamma ray exposure group.

Table. 8

COMPARISON OF LD 50/30 VALUE (X-RAY IRRADIATION)

STRAIN	SEX	NUMBER OF ANIMALS	AGE	LD 50-30	RANGE	CONFER
INZUCHT-STAMMES	MALE	360		196 r	210 - 184	1
INZUCHT-STAMMES	FEMALE	360		400 r	416 - 385	1
S.M.	MALE	72	40- 42	423 r	427 - 409	2
d.d.N.	FEMALE	77	40- 42	445 r	464 - 427	2
d.d.N.	MALE	72	40- 42	459 r	479 - 438	2
S.M.	FEMALE	81	40- 42	527 r	531 - 523	2
R.F.	FEMALE	120	63- 84	506 r	512 - 498	3
BALB/C	MALE	290	95-219	544 r	505 - 580	4
C57BL	MALE	168	107-174	618 r	580 - 642	4
A/He	MALE	148	91-142	632 r	603 - 650	4
A.C.F.I	MALE	118	89-120	649 r	632 - 665	4
C.A.F.I	MALE	556	91-231	656 r	623 - 735	4
C3H		307	94-137	665 r	610 - 710	4
N.M.R.I.	MALE	666	60- 80	717 r	709 - 725	5
N.M.R.I.	FEMALE	704	60- 80	778 r	771 - 785	5
B.A.F.I.	MALE	322	70-120	634 r	623 - 645	6
B.A.F.I.	MALE	308	70-120	663 r	654 - 672	7
B.A.F.I.	MALE	294	70-120	816 r	808 - 826	8

CONFER:

1. H. Langendorff et al
2. Miyagawa and Watanabe: 200 kvp. 25ma. H.V.L. 1.73mmPb. 62r/min. F.S.D. 50cm.
3. A.C. Upton et al : 250 kvp. 30ma. H.V.L. 0.55mmPb. 79.8r/min. F.S.D. 97cm.
4. Henry I. Kohn et al : 250kvp. H.V.L. 1.60mmPb. 35r/min.
5. W.H. Chapman et al : 2000kvp. no added filter. H.V.L. 4.3mmPb. 15r/min. at 200cm.
6. Dogglas Grahn et al : 250 kvp.
7. Dogglas Grahn et al : 135 kvp.
8. Dogglas Grahn et al : 80 kvp.

1. Female > Male (> 50%) 2. S.M. Female > Male (> 24%) 3. d.d.N. Male > Female (> 4%)
4. All strain Female > Male (> 4%) 5. N.M.R.I. Female > Male (> 6%)

IV. Conclusion

The relationship between mortality rate and radiation dose as biological subject was studied by using inbred mice of four strains and the following results were obtained.

1) Equation between mortality rate and dosage

a) Co^{60} gamma exposure group

CF#1 F $Y=4.9930+15.439\ (X-2.8545)$

CF#1 M $Y=4.9847+12.375\ (X-2.8608)$

CFW F $Y=5.1468+12.07\ (X-2.8703)$

CFW M $Y=5.544+16.941\ (X-2.8331)$

S.M F $Y=5.651+27.042\ (X-2.8714)$

S.M M $Y=4.8539+26.07\ (X-2.8668)$

ddN F $Y=5.0214+22.447\ (X-2.8651)$
ddN M $Y=4.6337+38.95\ (X-2.8673)$

b) X-ray exposure group

S.M F $Y=4.9855+12.38\ (X-2.7205)$
S-M M $Y=5.2502+4.313\ (X-2.6841)$
ddN F $Y=4.9264+13.753\ (X-2.6429)$
ddN M $Y=5.1917+10.102\ (X-2.6809)$

2) Comparison of dosages required to increase mortality rates by 10% wlthin the mortality rate range of 30 to 60% Co^{60} gamma ray exposure group

CFW strain		CF#1 strain		SM strain		ddN strain	
F	M	F	M	F	M	F	M
35 r	22 r	26 r	33 r	15 r	16 r	18 r	11 r

X-ray exposure group

SM strain		ddN strain	
F	M	F	M
25 r	54 r	19 r	26 r

3) Comparison of dosages required to increase the mortality rates by 10% within the various mortality rate groups when the dose required to increase the mortality rates within the range of 30 to 60% by 10% each is set at 1.0.

1-10%	10-20%	30-60%	70-80%	80-90%
3	1.5	1.0	1.5	2.0 (Co^{60} gamma)
3	1.5	1.0	1.5	2.0 (X-ray)

4) LD50/30 value

The LD50/30 values of the X-ray exposure group had a wider range than the Co^{60} gamma ray exposure group.

5) The male-female radiation sensitivity difference changes by strain and dosage.

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