A Model for Radiation Injury (8)
Kinetics of Acute Radiation Lethality

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放射線障害の模型（8） 急性死の解析

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約7,000匹のメダカを用いコバルト・ガンマ線の照射による急性死に関する統計的資料を得る実験を行つた．1回照射による線量と平均生存日数との関係を得るために 5.4KRから 104.2KRの範囲の10種類の線量を照射した．平均生存日数は1.0日から11.5日に及んだ．死亡数の日数分布は5.4KRから75.2KRまではピークが一つであるが，95.2KR では双峯性（bimodal）分布となつた．44.8KR の前照射後 LD_{50}（1.5時間）を経時的に求めた．その結果前照射後3日までは障害が回復も増巾もしないことが知られた．放射線感受性の個体差は前照射により，対照群より減少することも知られた．22.7KR，42.7KR および62.7KRの三つの前照射線量について48時間後に LD_{50}（1.5時間）を求めると，前照射による百分率残留障害（per cent residual injury）は前照射線量に殆ど依存しないことが知られた．42.7KRの線量を種々の間隔で2回照射した実験結果は障害の加法性を示唆した．95.1KRから 150.7KRの範囲で1回照射を行い，1時間々隔で死亡数分布を測定すると，日数分布の場合と同様にある線量範囲で双峯性分布が得られた．39.5KRの前照射後48時間に大線量照射を行い LD_{50}（1時間）から LD_{50}（12時間）までの12個の LD_{50} を求めこれを対照群と比較した．以上の結果を従来の二回照射法によらずに指数関数模型を用いて解釈を試みた．その結果1回照射による障害の経時的変化についての推定が可能となつた．

I. Introduction

The problem of recovery in radiation injury has sometimes been thrown into confusion owing to the variety of definitions of radiation injury. Classical definition of the injury is given by a difference of $LD_{50}(30)$s between control and previously irradiated groups, so-called paired-dose method[1-10]. Some modification on paired-dose method will be done by replacing single test dose with duration-of-life exposure[11]. In this case the whole body injury is evaluated from a difference of mean after survival between control and previously irradiated groups. These two definitions have an ambiguity on the time when the residual injury must be referred[12][13]. It comes from the fact that the time of exposure to the test dose is not identical with the time at death. Assuming the time pattern of the whole body injury, the method to test the validity of the assumption with the experimental data may be called an indirect definition of the whole body injury. Much of works in this line have been done with assumption of exponential recovery function[14-22]. Most elegant method to determine the whole body injury has been proposed by Brues

et al[23-27]. It has given the way how to calculate the whole body injury from mean survival time under duration-of-life exposure. In acute radiation death, the daily death distribution is sometimes clearly bimodal[23-30] and mean survival time of the distribution is hardly determined as a good statistic.

In the previous paper[31] a vector-matrix representation of the whole body injury has been presented. In the mathematical representation the whole body injury is constructed with the injuries of each organ and the interactions among the organs. The formula for the whole body injury is as follows,

$$I_w=\sum_{i=1}^{n} w_i\left(I_{ii}+\sum_{j=i}^{n} A_{ij}I_{jj}+\sum_{j=k}^{n} B_{ij}A_{jk}I_{kk}+\sum_{j,k,1}^{n} B_{ij}B_{jk}A_{k1}I_{11}+\cdots\right.$$

I_w: Whole body injury

I_{ii}: Intrinsic injury of the i-th organ

A_{ij}, B_{ij}: Interaction from the j-th organ to the i-th organ

W_i: Essentialness of the i-th organ to survive

7723 fish were used to obtain acute lethality data following single and paired doses. In this communication the author presents a time pattern of acute radiation injury inferred from the statistics of the acute mortality.

II. Dosimetry measurements

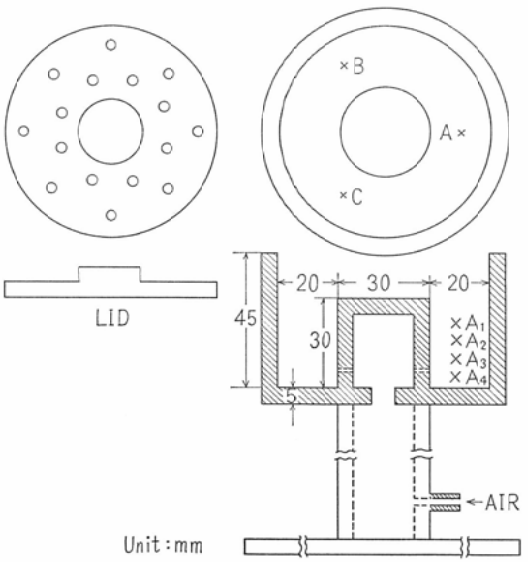
Dosimetry measurements were done by Fluoroglass Dosimeter (developed by Tokyo Shibaura Electric Co., Japan). The silver-activated phosphate glasses, Type FD-Rl-1 (1 mmϕ × 6 mm), were placed in the exposure cage shown in Figure 1 with lucite holder and after filling the cage with water gamma-rays of Co^{60} were delivered to the cage lidded. Each glass washed with chromic acid mixture and with distilled water was inspected by microscope for cracks and about 10% of the glasses were discarded before exposure. The fluorescence measuring device was Type FGD-3B. To avoid an error from build-up and fading of luminescence the exposed fluoroglasses were kept at 25°C and 24 hours after the exposure the fluorescence was measured. Just before the measurement of the fluorescence the glasses were washed again by the standardized method. The calibrations of the glasses were done in the gamma-rays of Co^{60} with relatively low dose-rate by the Probe, No. 606, of Radocon calibrated at Electro-Technical Laboratory, Japan. The cobalt source of 3×10^3 curies used in these experiments was cylindrical and the exposures were done within the cylinder. When the exposure starts, the source comes down slowly to the pre-setted position through shutter of mercury and then it stops there. After the end of exposure the source goes up again to its container. Therefore the dose delivered during the movement of the source before and after each exposure was corrected when the exposure time was short. The radioactive decay of the cobalt source was also corrected. In the course of experiments the cobalt source was replaced by

TABLE I Dose distribution in the exposure cage

Positions in Fig. 1	Mean dose (kR)	Positions in Fig. 1	Mean dose (kR)
A_1, B_1 and C_1	3.70± 0.1	A_1, A_2, A_3 and A_4	3.50± 0.1
A_2, B_2 and C_2	3.60± 0.1	B_1, B_2, B_3 and B_4	3.55± 0.1
A_3, B_3 and C_3	3.30± 0.1	C_1, C_2, C_3 and C_4	3.25± 0.1
A_4, B_4 and C_4	3.15± 0.1		

more radioactive one and the dosimetry measurements and their calibration were repeated for the new cobalt source with the same method as before. The dose-rate of the old cobalt source was 7.4 ± 0.1 kR/min. The dose-rate of the new cobalt source was 10.0 ± 0.1 kR/min. An example of the dose distribution within the exposure cage was shown in Figure 1 and in Table I. There were significant differences in some points. Since the fish were free to swim in the cage, an average value of the doses was assigned to them.

Figure 1. Lucite cage used for irradiation



III. Material and Method

The animals used in these experiments were medaka, Oryzias latipes. Each time about 10^3 to 3 × 10^3 fish were purchased and the stock numbers were given to them. At the time purchasing, each stock was treated with metylene blue solution to prevent from bacterial infection. They were bred in the open air for several weeks before exposures to avoid any shipping stress. Any series of experiments except the Experiment 1 in the text was tried to complete within the same stock including any kind of controls, since large variances between the stocks were expected. The exposures were done by the Lucite cage shown in Figure 1. In each exposure, 30 fish were free to swim within the cage filled with water and lidded. The water in the cage was being bubbled with fresh air during exposure. After the exposure the fish were bred in plastic cages containing 2.5 liters of water in groups of twenty in a room equipped with a forced-air ventilation system and the temperature of the water was kept at 23°C. The water in the breeding cage was refreshed every day. Control groups were shammed once and specially twice for paired exposures. The fish were fed with freshwater oligochaetes ad libitum. The carcasses were counted and removed every day. Survival times were recorded according to the convention that an animal lived to the end of the interval in which it died. Exposed groups were observed until all the animals died and usually it took less than 20 days. The control groups were ordinarily observed up to 30 days after their sham exposures.

The LD_{50} determinations were made by exposing groups to graded gamma-ray dosages and deter-

mining the survival. A probit transformation of percentage mortality was used to compute the LD_{50} as described by Mather[32].

Sham exposure itself has given no significant excess mortality in 30 days compared with that of control without sham exposure. But there might be a possibility that an effect of sham exposure on mortality may be detected by additional actual exposure. In order to evaluate the effect, following experiments were done. Two groups shammed were irradiated with dose of 22.7 kR or 82.7 kR. A group shammed was used for determination of LD_{50} (1.5 hours). The mean survival times and the LD_{50} of the above groups were compared with those of other similar groups without sham exposure. There was no significant difference between them.

IV. Results

Experiment 1. Dose-Survival Time

The doses ranging from 5.4 kR to 102.4 kR were given to the fish to estimate the whole body injury. The dose-rate was 7.4 kR/min. The mean survival times were given in Table II with the number of animals.

TABLE II Dose and mean survival time (MST) for single exposure

Dose (kR)	No. of animals	MST±SE (days)	Dose (kR)	No. of animals	MST±SE (days)
Control	169	(≫30)	60.5	278	7.5± 0.1
5.4	211	11.5± 0.1	75.2	270	6.0± 0.1
9.1	207	10.3± 0.1	89.9	241	4.2± 0.1
16.1	258	9.7± 0.1	95.2	209	2.6± 0.1
31.1	300	8.7± 0.1	102.4	229	1.0± 0.1
45.8	317	8.4± 0.1			

All the mean survival times are significantly different one another with $p=0.01$. Plotting them in log-log grid one can see almost dose-independent survival times in the dose rage from 10 kR to 50 kR as shown in Figure 2. Their temporary death distributions were also shown in Figure 3. There appeared bimodal distribution in 95.2 kR and the distribution was fairly well reproducible.

Experiment 2. LD_{50} (1.5 hours) as a Function of Time

LD_{50} (1.5 hours)s were determined to evaluate the whole body injury induced by sublethal conditioning dose. In probit analysis doses are ordinarily plotted either in logarithmic scale or in linear scale. In order to see which scale of them may give a better linear regression, nine groups of each thirty fish were irradiated with different doses. The results have shown that both scales give comparable linearity of mortalities in probit and then linear scale for dose was used for all analyses in probit. Giving 44.8 kR of conditioning dose, LD_{50} (1.5 hours)s were determined as a function of time as shown in Table III. Namely, the interval between the conditioning dose and the test dose covered one day to four days. The dose-rate was 7.4 kR/min. Residual injury was calculated as a difference from LD_{50} (1.5 hours) of control as the conventional paired-dose method. One cannot follow the time course further because death may happen with the conditioning dose itself beyond the fifth day. These characteristics mentioned above were reconfirmed by experiment of same scale. Experiments with the conditioning dose of 16.4 kR were done without any definite results. The conditioning dose of 16.4 kR seemed too low compared with experimental error.

Experiment 3. LD_{50} (1.5 hours) as a Function of Conditioning Dose

Figure 2. Dose-survival curve from single exposure

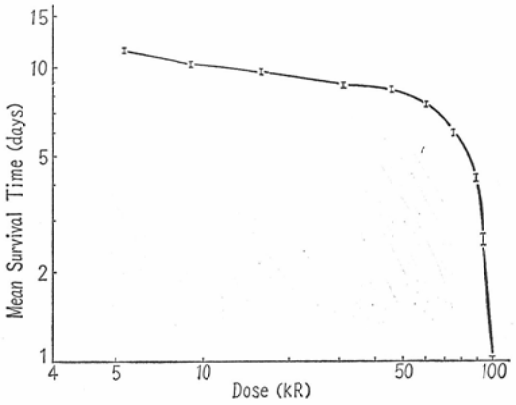


Figure 3. Temporary death distribution from single exposure

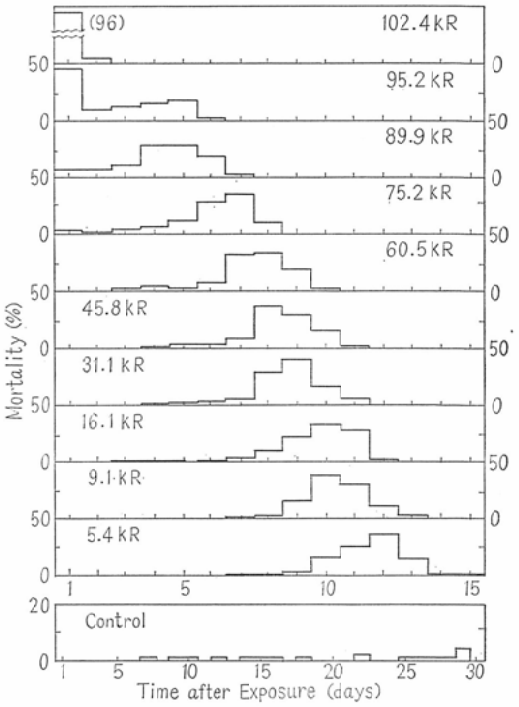


TABLE III LD_{50} (1.5hours), regression coefficient and residual injury after conditioning dose of 44.8 kR

Days after conditioning dose	No. of animals	LD_{50}(1.5)±SE (kR)	Regression coefficient±SE (1/kR)	Residual injury (kR)
Control	690	129.5± 1.1	0.051± 0.004	0
1	149	87.3± 1.6	0.106± 0.016	42.2
2	120	85.1± 1.4	0.121± 0.017	44.4
3	116	86.1± 1.7	0.100± 0.016	43.4
4	120	82.3± 1.5	0.109± 0.014	47.2

TABLE IV LD_{50} (1.5 hours), regression coefficient and residual injury at 48 hours after various conditioning doses

Conditioning dose (kR)	No. of animals	LD_{50}(1.5)±SE (kR)	Regression coeffcient ± SE (1/kR)	Residual injury (kR)
0	690	129.5± 1.1	0.050± 0.004	0
22.7	121	97.4± 1.2	0.128± 0.017	32.1
42.7	120	83.9± 1.5	0.097± 0.016	45.6
62.7	112	69.3± 1.9	0.113± 0.019	60.2

In order to estimate a dependence of the residual injury on the conditioning dose, various conditioning doses were given to the animals and 48 hours after the conditioning dose LD_{50} (1.5 hours)s were

TABLE V Mean survival time (MST) after fractionated exposure by a variable time interval

Dose (kR)	Time interval (days)	No. of animals	MST ± SE (days)
42.7		120	12.7± 0.1
42.7+42.7	0	121	8.0± 0.2
42.7+42.7	1	116	9.4± 0.2
42.7+42.7	2	120	10.3± 0.2
42.7+42.7	3	115	10.7± 0.2
42.7+42.7	4	120	10.4± 0.1
42.7+42.7	5	117	11.7± 0.1
42.7+42.7	6	118	10.7± 0.1
Shammed	2	60	(⩾30)

TABLE VI Number of animals and doses

Single dose		Paired-dose	
No. of animals	Dose (kR)	No. of animals	Dose (kR)
147	95.1	152	39.5+76.6
148	104.3	149	39.5+85.8
149	113.6	148	39.5+95.1
152	122.9	149	39.5+104.3
148	132.1	149	39.5+113.6
149	141.4		
149	150.7		

determined. The dose-rate was 10 kR/min. The data obtained were shown in Table IV.

Experiment 4. Temporary Death Distribution after Fractionated Exposure.

To estimate an additivity of the whole body injuries, mean survival times were determined with irradiation of two equal doses in variable time interval and also an attention was paid to their temporary death distributions. Dose per irradiation was 42.7 kR and dose-rate was 10 kR/min. Time interval between the first and the second dose covered from one day to six days after the first dose. The interval could not be extended over six days because death occured with only the first dose. Data obtained were shown in Table V. A point-by-point t test with $p=0.01$ on mean survival time showed that there was no significance between groups of two- and six-day interval except five-day interval. The temporary death distributions of the above groups were shown in Figure 4 and one can see bimodal distributions in the groups of shorter time interval. Significant increase of mean survival time in five-day interval was hardly interpretable. The same experiments were repeated with different stock of animals and the characteristics mentioned above were fairly well reproducible except increase of mean survival time in five-day interval. With 22.7 kR per exposure the same type of experiments were done but the data obtained were nothing definite.

Experiments 5. Temporary Death Distribution in Twelve Hours after Exposure

To see a fine structure in the first day death in Figure 3, observations were done in one-hour interval after massive single or paired doses. In paired doses the second dose was given in 48 hours after the first dose. The observation period covered twelve hours. The results were shown in Table VI and in Figure

Figure 4. Tempory death distribution from fractionated exposure. Arrows indicate the days on which the second doses were delivered.

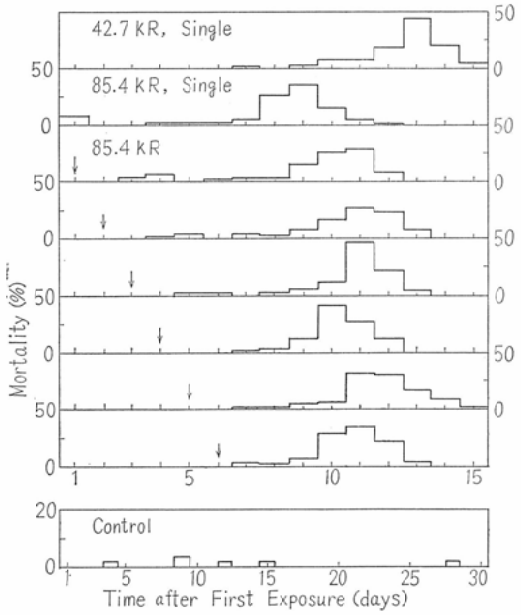


Figure 5. Temporary death distribution from single exposure

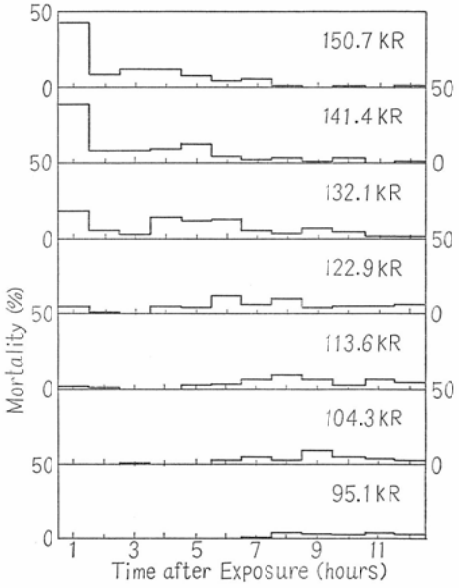


Figure 6. Temporary death distribution from fractionated exposure Time is measured from the second exposure.

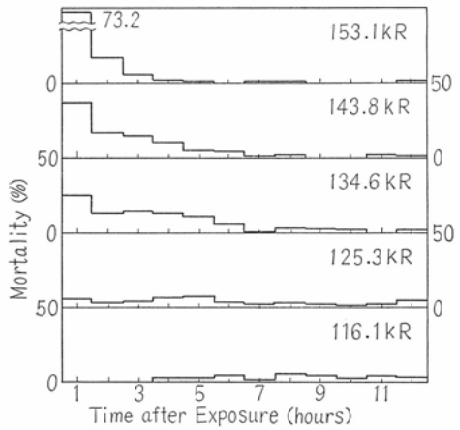
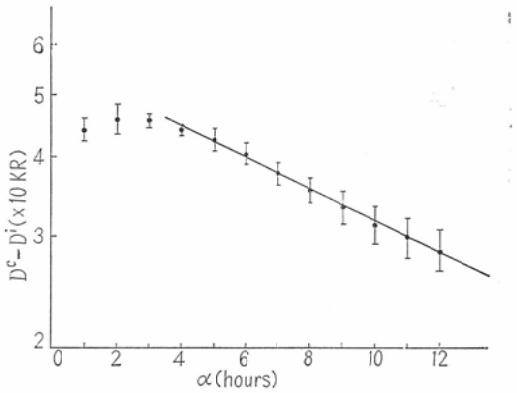


Figure 7. Residual injury as function of observation period α



5 and 6. With these data LD_{50} (α)s were calculated for twelve αs and the values were shown in Table VII. The residual injuries were plotted in Figure 7.

V. An Interpretation and Discussions

The data obtained by these experiments were analysed by an exponential model, the details of which were shown in the Appendix. The whole body injury induced by a massive exposure may change daily in a complicated manner in the post-irradiation period. There may be not only recovery but also amplifi-

TABLE VII LD_{50} (α)s of control and irradiated groups for various α

	No. of animals	α (hours)	LD_{50} (α)±SE (kR)	Regression coefficient±SE (1/kR)	Residual injury (kR)
Control	895	1	150.5± 1.6	0.053± 0.005	
Irradiated	747	1	106.5± 0.9	0.076± 0.006	44.0± 1.8
Control	895	2	146.2± 2.3	0.058± 0.009	
Irradiated	747	2	100.5± 0.7	0.087± 0.006	45.7± 2.4
Control	1042	3	142.1± 0.9	0.066± 0.005	
Irradiated	747	3	96.6± 0.6	0.095± 0.006	45.5± 1.1
Control	1042	4	137.4± 0.8	0.073± 0.004	
Irradiated	747	4	93.3± 0.6	0.093± 0.006	44.1± 1.0
Control	1042	5	133.2± 1.2	0.077± 0.008	
Irradiated	747	5	90.6± 1.3	0.094± 0.012	42.6± 1.8
Control	1042	6	129.1± 0.1	0.073± 0.004	
Irradiated	747	6	88.6± 1.4	0.093± 0.013	40.5± 1.6
Control	1042	7	125.8± 0.8	0.070± 0.004	
Irradiated	747	7	88.1± 1.3	0.096± 0.012	37.7± 1.5
Control	1042	8	122.1± 0.8	0.064± 0.003	
Irradiated	747	8	86.6± 1.4	0.096± 0.013	35.5± 1.6
Control	1042	9	118.8± 0.8	0.058± 0.003	
Irradiated	747	9	85.4± 1.7	0.092± 0.015	33.4± 1.9
Control	1042	10	116.2± 0.8	0.060± 0.003	
Irradiated	747	10	84.8± 1.9	0.089± 0.015	31.4± 2.1
Control	1042	11	113.9± 0.9	0.057± 0.003	
Irradiated	747	11	83.9± 2.0	0.088± 0.018	30.0± 2.2
Control	1042	12	111.5± 0.9	0.059± 0.003	
Irradiated	747	12	82.8± 1.9	0.090± 0.017	28.7± 2.1

TABLE VIII Dose and median survival time

Dose (kR)	Median survival time (days)	Dose (kR)	Median survival time (days)
9.1	9.8	60.5	7.1
16.1	9.4	75.2	5.9
31.1	8.3	89.9	4.0
45.8	7.9	95.2	3.4

cation of the injury. The essential assumption in the model is that any change in the injury may be approximated by proper exponential functions as shown in Figure A of the Appendix. As for a sensitivity variation in the population, an animal which dies at the median survival time was chosen as a representative animal.

Experiment 1. Dose-Survival Time

In the bimodal region conventional median survival time sometimes falls between two peaks in the temporary death distribution. Below 95.2 kR more than fifty percent of animals died in the second mode. Therefore median survival times in the dose range were calculated within the second mode, namely from

the sub-population where deaths in the first day were excluded. These values were tabulated in Table VIII.

From a relation between median survival time (α) and ln dose, following amplification constants were estimated by using equation (A4) in the Appendix.

$\alpha \geqq 7.4$ days

$$\alpha = 13.1 - 1.399 \ln \text{dose} \quad (1)$$

$$\lambda = 0.71 \pm 0.12 \text{ day}^{-1} \quad (2)$$

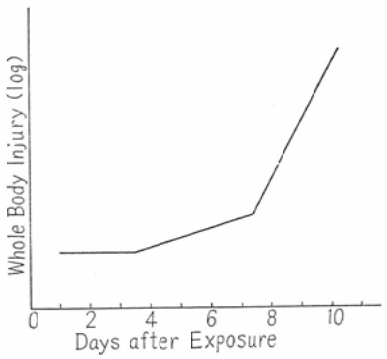
$\alpha \leqq 7.4$ days

$$\alpha = 41.1 - 8.249 \ln \text{dose} \quad (3)$$

$$\lambda = 0.121 \pm 0.005 \text{ day}^{-1} \quad (4)$$

On the other hand LD_{50} (1 day) = 95.6 kR was substituted to equation (3) and then α became 3.5 days. Accordingly the whole body injury induced by a massive single exposure is estimated as shown in Figure 8. In the period of the first day to 3.5th day the injury was estimated from Experiment 2.

Figure 8. A whole body injury by single exposure



Experiment 2. LD_{50} (1.5 hours) as a Function of Time

The dependence of the difference in LD_{50} (1.5 hours)s on the time, t^1 is given in equation (A8) in the Appendix where the notations were given. In the period of the first to the third day, λ is estimated to be zero, namely no recovery and no amplification. On the other hand, many works on mammals[3)7)8)33-36)] have shown a recovery in the period by the conventinal paired-dose method. As was discussed in the previous papers[12)13)], the interpretations of the above data on mammals are quite doubtful. An increase of D^c-D^i in the fourth day may correspond to the amplification of $\lambda = 0.12$ day^{-1} in Figure 8. It should be emphasized that no recovery and no amplification ($\lambda = 0$) is concluded with

$$\frac{\partial (D^c - D^i)}{\partial t^1} = 0 \quad (5)$$

In the conventional paired-dose method, no recovery and no amplification is concluded from the fact that $D^c - D^i = D_o$ where D_o is conditioning dose. In the exponential model in the Appendix necessary and sufficient condition for $\lambda = 0$ is equation (5).

As was seen in Table III the regression coefficents of divided exposures were larger than that of single exposure (control). Since a reciprocal of the regression coefficient in the probit analysis reasonably gives a measure on the fluctuation of sensitivity in the population[37-39)], data on these experiments show

that the conditioning dose decreased the fluctuation of sensitivity in the population. On the contrary there is a positive relationships between the regression coefficient and LD_{50} (30 days) among the strains of mice[37)38)]. Exactly speaking LD_{50} and its regression coefficient may depend on dose-rate[30)40)]. Therefore the general measure on the fluctuation of sensitivity in the population may be obtained from the regression coefficient of LD_{50} which is limiting value when exposure time tends to zero.

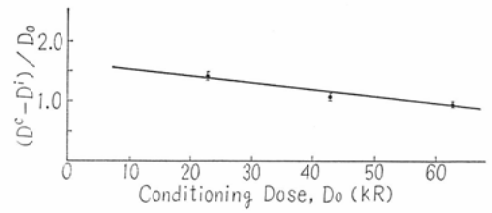
Experiment 3. LD_{50} (1.5 hours) as a Function of Conditioning Dose

From equation (A8) in the Appendix, the following equation holds.

$$\frac{\partial}{\partial D_0}\left(\frac{D^c-D^i}{D_0}\right)=0 \qquad (6)$$

Namely, the ratio $(D^c - D^i)/D_0$ is expected to be independent from D_0. In Figure 9 D_0 versus $(D^c - D^i)/D_0$ is plotted. A linear regression line was calculated by the method of least squares. The regression coefficient ($= -0.01125\ kR^{-1}$) was not significant from zero with $p = 0.05$ by analysis of vari-

Figure 9. Percent residual injury as function of conditioning dose



ance. Accordingly these data were not enough to show any dependency of $(D^c - D^i)/D_0$ upon D_0 and were still consistent with the exponential model. On the other hand most of data on mammals[8)33)35)36)] have shown some dependences of the residual injury on the conditioning dose.

Experiment 4. Temporary Death Distribution after Fractionated Exposure with Variable Time Interval

A bimodality in the temporary death distributions was seen even in the fractionated exposure. This may also suggest no recovery and an additivity of the injuries[22)41)42)]. Single dose of 42.7 kR did not induce any bimodal distribution and if the animal recovered completely from the first dose, the second dose of 42.7 kR would not induce any bimodal distribution. However, the distributions were hard to be analysed quantitatively.

An apparent discrepancy in mean survival time was seen between Table II and Table V. The experiments in Table II were done in spring in 1965 and the experiments in Table V were done in winter in 1965. The discrepancy may be due to seasonal effect and (or) to variation between the stocks.

Experiment 5. Temporary Death Distribution in Twelve Hours after the Exposure.

The bimodality in the temporary death distribution in twelve hours from single exposure also suggests that the pattern of the whole body injury in the period may be similar to that in Figure 8 with different time scale. An analysis such as in Experiment 1 was not shown in this paper since the calculated regression coefficient was not significant with $p = 0.05$. If one will extend the observation period to twenty-four hours, one might have a significant regression coefficient.

As shown in Figure 7, the residual injury is highly dependent upon the observation period, α. Then there happens a difficulty to assign a recovery or an amplification of the whole body injury by the con-

ventional paired-dose method. For example, if one takes $\alpha = 2$ hours, the residual injury is larger than the conditioning dose and the injury might be amplified. On the other hand if one takes $\alpha = 10$ hours, the residual injury is smaller than the conditioning dose and the injury might recover. A linear regression for $\alpha \geq 4$ hours was calculated with high significance as follows,

$$D^c - D^i = 66.7e^{-\lambda\alpha}$$
$$\lambda = 0.057 \pm 0.01 \text{ hour}^{-1} \quad (7)$$

The above equation has the same form as predicted by equation (A9) in the Appendix. However there is still a problem in an application of equation (A9) to this experiment, since no consideration was given to the bimodality seen in Figure 5 in the calculation of $LD_{50}(\alpha)$s.

Summary

Survival data were obtained on 7723 fish received Co^{60} gamma radiation of single or divided exposures. Single dose ranged from 5.4 kR to 104.2 kR and mean survival time ranged from 1.0 to 11.5 days. Their temporary death distributions were unimodal in range from 5.4 kR to 75.2 kR and the peak of the distribution shifted gradually to earlier period with dose. A dose of 95.2 kR produced a bimodal pattern in the temporary death distribution.

LD_{50} (1.5 hours)s were determined after conditioning dose of 44.8 kR. They showed that no recovery and no amplification seemed to happen up to the third day. The standard deviation of fluctuation of sensitivity in the population was decreased by the conditioning dose. Percent residual injury at 48 hours after conditioning dose ranging from 22.7 kR to 62.7 kR was almost independent upon each conditioning dose. An experiment of irradiation of two equal doses in variable time intervals has given some evidence on the additivity of two injuries.

A bimodality in the temporary death distribution was seen even in twelve hours of post-irradiation period after single massive exposure. The difference of LD_{50} (α)s between control and pre-irradiated groups were calculated as a function of the observation period, α. To these data an interpretation was given with an exponential model.

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Appendix

In the previous paper (F. Sato et al.: Nippon Acta Radiologica Vol. 27, No. 4, 1966) we have given some theoretical consideration on the paired-dose method. Basing on an exponential model some more generalized forms of the paired-dose method will be discussed below. The assumptions used were as follows.

1. In fractionated exposure the whole body injury of each exposure is additive one another at any time.

2. When the whole body injury of an animal accumulates to the lethal threshold, the animal will die.

3. The whole body injury increases or decreases exponentially. Recovery or amplification constants λ_n are assumed as follows.

$$\lambda_i \gtrless \begin{cases} \lambda_1 & \text{for} \quad 0 \leqq t \leqq t_1 \\ \lambda_2 & \text{for} \quad t_1 \leqq t \leqq t_1 + t_2 \\ \vdots & \vdots \\ \lambda_n & \text{for} \quad \sum_{i=1}^{n-1} t_i \leqq t \leqq \sum_{i=1}^{n} t_i \\ 0 & \text{for} \quad i=1, 2, 3, \cdots, n, \end{cases}$$

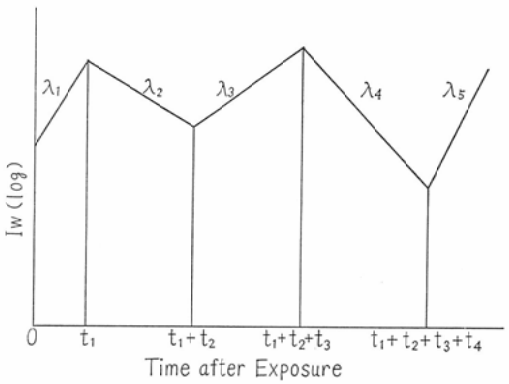
Then the whole body injury from single exposure will be given by the following equation.

$$I_w(D, t) = D \left(\prod_{i=1}^{n-1} e^{\lambda_i t_i} \right) e^{\lambda_n \left(t - \sum_{i=1}^{n-1} t_i\right)} \tag{A1}$$

$$\sum_{i=1}^{n-1} t_i \leqq t \leqq \sum_{i=1}^{n} t_i \tag{A2}$$

The equation (A1) was graphically shown in Figure A.

Figure A. An example of the whole body injury



A population of experimental animals has a sensitivity variation. The animal which dies at the median survival time in the population will be chosen as a representative animal and we will consider the whole body injury of the above representative animal. In the region $\lambda_n > 0$, a relation between dose and median survival time will be obtained as follows,

$$I_w(D, \alpha) = D \left(\prod_{i=1}^{n-1} e^{\lambda_i t_i} \right) e^{\lambda_n \left(\alpha - \sum_{i=1}^{n-1} t_i\right)} = I_L \tag{A3}$$

where
- D : Dose which gives a median survival time of α
- α : Median survival time
- I_L : Lethal threshold

From the equation (A3),

$$\lambda_n \alpha = \ln \left\{ I_L \left(\prod_{i=1}^{n-1} e^{-\lambda_i t_i} \right) e^{\lambda_n \sum_{i=1}^{n-1} t_i} \right\} - \ln D$$

$$\alpha = A - \frac{1}{\lambda_n} \ln D \tag{A4}$$

$$A \equiv \frac{1}{\lambda_n} \ln \left\{ I_L \left(\prod_{i=1}^{n-1} e^{-\lambda_i t_i} \right) e^{\lambda_n \sum_{i=1}^{n-1} t_i} \right\}$$

If the test (or second) dose is given on time t^1, the following equation holds.

$$I_w(D_o, t^1 + \alpha) + I_w(D^i, \alpha) = I_w(D^c, \alpha) = I_L \tag{A5}$$

where
D_o: Conditioning dose
D^c: $LD_{50}(\alpha)$ of control group
D^i: $LD_{50}(\alpha)$ of pre-irradiated group
t^1: Time when test dose D^i is given
α: Median survival time
I_L: Lethal threshold

From the equations (A1) and (A5),

$$D_o\left(\prod_{i=1}^{n-1} e^{-\lambda_i t_i}\right) e^{\lambda_n (t^1 + \alpha - \sum_{i=1}^{n-1} t_i)} + D^i \left(\prod_{i=1}^{n'-1} e^{\lambda_i t_i}\right) e^{\lambda_{n'} (\alpha - \sum_{i=1}^{n'-1} t_i)}$$

$$= D^c \left(\prod_{i=1}^{n'-1} e^{\lambda_i t_i}\right) e^{\lambda_{n'} (\alpha - \sum_{i=1}^{n'-1} t_i)}$$

$$\sum_{i=1}^{n-1} t_i \leqq t^1 + \alpha \leqq \sum_{i=1}^{n} t_i, \quad \sum_{i=1}^{n'-1} t_i \leqq \alpha \leqq \sum_{i=1}^{n'} t_i \tag{A6}$$

The difference of $LD_{50}(\alpha)$s between control and pre-irradiated groups is expressed as follows.

$$D^c - D^i = D_o \times \left\{ \frac{\left(\prod_{i=1}^{n-1} e^{\lambda_i t_i}\right) e^{\lambda_n (t^1 + \alpha - \sum_{i=1}^{n-1} t_i)}}{\left(\prod_{i=1}^{n'-1} e^{\lambda_i t_i}\right) e^{\lambda_{n'} (\alpha - \sum_{i=1}^{n'-1} t_i)}} \right\} \tag{A7}$$

To see a dependency on t^1 or on α, the following forms will be suitable.

$$D^c - D^i = D_o \left(\prod_{i=n'}^{n-1} e^{\lambda_i t_i}\right) e^{\lambda_n (\alpha - \sum_{i=1}^{n-1} t_i)} e^{-\lambda_{n'} (\alpha - \sum_{i=1}^{n'-1} t_i)} e^{\lambda_n t^1} \tag{A8}$$

or

$$D^c - D^i = D_o \left(\prod_{i=n'}^{n-1} e^{\lambda_i t_i}\right) e^{\lambda_n (t^1 - \sum_{i=1}^{n-1} t_i)} e^{\lambda_{n'} \sum_{i=1}^{n'-1} t_i} e^{(\lambda_n - \lambda_{n'}) \alpha} \tag{A9}$$

where

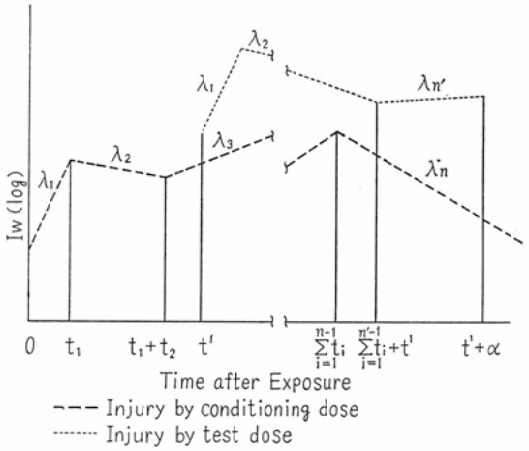
$$\sum_{i=1}^{n-1} t_i \leq t^1 + \alpha \leq \sum_{i=1}^{n} t_i, \quad \sum_{i=1}^{n'-1} t_i \leq \alpha \leq \sum_{i=1}^{n'} t_i$$

$\lambda_{n'} > 0$

The relations among n, n′, and $t^1 + \alpha$ are illustrated in Figure B.

The equations (A8) and (A9) will be interpreted as follows. If one changes the time t^1 with fixed α, one can obtain an estimation of λ_n from the equation (A8). If $\lambda_n < 0$, the whole body injury by the conditioning dose is recovering with constant λ_n in the period around $t^1 + \alpha$ where t^1 is variable. If $\lambda_n > 0$, the injury is amplifying. On the other hand, if one makes α variable with constant t^1, one can obtain an estimation of $(\lambda_n - \lambda_{n'})$ from the equation (A9). An experiment which may give the dependencies of $D^c - D^i$ on both t^1 and α, will be desirable for estimation of λ_n and t_n where n = 1, 2, 3,...

Figure B. Whole body injuries by paired-dose



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