FROM THE RADIOBIOLOGICAL DIVISION OF THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, DEPT. 1, SUNDBYBERG, SWEDEN.

PROTECTIVE EFFECT OF CYSTEAMINE AT FRACTIONATED IRRADIATION

I. Lethality up to 30 days after last irradiation

by

ARNE NELSON, OLA HERTZBERG and INGA-BRITT HENRICSSON

A considerable amount of information is accumulating on the protective merits of numerous chemical compounds in acute injuries, measured as lethality, caused by single whole body irradiation (reviewed by ELDJARN & PIHL (1960), and others). Few attempts have, however, been made to investigate the effect of protective substances at fractional irradiation up to accumulated lethal doses, or at continuous long term irradiation.

PATT et coll. (1953) investigated the protective effect of cysteine on mice by using a split-exposure technique. The interval between successive radiation fractions did not, however, exceed 5 min. The two fractions varied from 100 to 700 r and the amount of cysteine injected was proportional to the radiation dose. PATT concluded from his results that irradiation prior to cysteine administration does not influence the protection against subsequent exposure, and that the lethal potential of small dosages of radiation cannot be reversed by cysteine under these conditions.

RUGH & CLUGSTON (1954) could not observe any protective effect of cyste-

Submitted for publication 15 February 1963.

amine on mice given 100 r per day. The protected mice died after an average accumulated dose of 1 230 r, the corresponding value for the controls being 1 440 r. LANGENDORFF & CATSCH (1956) gave two doses of 175 to 500 r with 24 hour intervals and found a protective effect of cysteamine, which, however, was less than that with single doses. Later LANGENDORFF et coll. (1959) tested the effect of serotonin. They gave three fraction doses of 505 to 1 100 r with 30 day intervals and 750 to 1 050 r with 15 day intervals and observed a good protective effect. NOBLE et coll. (1960) gave ten daily doses of 50 to 200 r to mice and noticed a protective effect with AET. DOULL et coll. (1960) in a similar investigation observed a significant reduction in the 30 day mortality with serotonin and dimethyldithiocarbamide acid, but no effect with cysteamine.

The few studies on the protective effects obtained have resulted in equivocal results due to the rather limited range of fraction doses, intervals and accumulated doses; it is likely that an investigation with a wider range would give valuable information concerning the mechanisms of protection and of recovery, and an answer to the question whether the chemical protection is due to a 'dose reduction' effect, or to an enhanced recovery, might perhaps be obtained.

The present investigation is an attempt to elucidate some of these problems.

Material and Methods

Animals. In all experiments only male mice of an inbred CBA strain were used. Their age was 60 to 70 days at the first irradiation.

Irradiation conditions. The roentgen apparatus was operated at 260 kV and 10 mA, filter 0.5 mm Cu, inherent filtration 4 mm Al, dose rate 84 r/min, distance between the roentgen tube and the object approximately 40 cm.

The animals were irradiated in groups of ten in a plastic 'wheel' and were then placed together in a cage. Because of the growth of the animals during the experimental period, single animals were suffocated in the radiation wheel. The area of the breathing holes in the wheels was therefore increased to give the animals ample air supply; this possibly influenced the radiosensitivity. This change was made between two series of experiments in August 1961, but one group (160 r, 7 days) was carried through at the changed conditions.

The irradiation schedule, giving fractionated doses, accumulated doses, and intervals, is presented in Tables 1 to 7.

Groups of animals consisting of about 60 mice were exposed under the same irradiation conditions. Half the number received an intraperitoneal injection of 3 mg cysteamine 15 min before the irradiation.

Controls. In several of the untreated control groups, each consisting of 50 mice, no deaths occurred during the observation time, which in some cases was extended to 11 months.

Table 1

Mortality after fraction dose 80 r — time interval 1 day (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
13.2.62	640	30	30							30	0
	640	*30*	*27*					*1*		*26*	*13.3*
	960	30	30	1						29	3.3
	960	*30*	*29*							*29*	*3.3*
	1 280	30	30	2	2	2				24	20.0
	1 280	*30*	*23*	*2*	*1*					*20*	*33.3*
	1 600	30	27	9	8	4	2			4	86.6
	1 600	*30*	*17*	*2*	*1*				*1*	*13*	*56.7*
	1 920	30	15	13	1	1				0	100.0
	1 920	*30*	*13*	*2*	*3*	*3*				*5*	*83.2*
28.8.62	640	20	20							20	0
	800	20	20							20	0
	960	20	20			1				19	5.0
	1 120	20	19							19	5.0
	1 280	20	20	4	1					15	25.0
	1 440	20	17	3	2					12	40.0
	1 600	20	11	5						6	70,0
	1 760	20	8	4	3					1	95.0

The toxicity of cysteamine was tested in some non-irradiated groups. Of 50 mice, receiving cysteamine every day for 24 days, 48 survived, and out of 49 mice, injected once a week for more than 40 weeks, 46 survived.

A mathematical model (see below), based on the results of the first series in 1960—1961, was designed and used for an extended examination in 1961—1962. Complementary experiments were carried out during the autumn of 1962 in order to obtain further confirmation of the applicability of the mathematical model.

The mortality in the early series was observed up to only 30 days after the last irradiation. The observation in the later series was extended to the life-span of the animals. Only the 30 day mortality is reported in this paper, however.

Results

The results of the experiments are presented in Tables 1 to 7; they are reported upon in groups, defined by a certain fraction dose at a given interval.

Table 2

Mortality after fraction dose 160 r — time interval 1 day (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
17.1.62	480	30	30							30	0
	480	*30*	*30*							*30*	*0*
	800	30	30		3	3				24	20.0
	800	*30*	*30*		*1*					*29*	*3.3*
	1 120	30	30		24	4				2	93.2
	1 120	*30*	*30*		*13*	*3*				*14*	*53.3*
	1 440	30	30	6	24					0	100.0
	1 440	*30*	*29*	*6*	*23*					*0*	*100.0*
	1 760	30	30	26	4					0	100.0
	1 760	*30*	*22*	*19*	*3*					*0*	*100.0*
28.8.62	480	20	20							20	0
	800	20	20							20	0
	1 120	20	20		15	2				6	70.0
	1 440	20	20	5	13	2				0	100.0

1. *Fraction dose 80 r, interval 1 day* (Table 1). No conclusions can be drawn regarding any protective effect against radiation from the series in which cysteamine has been tested. It is, however, apparent that the protected animals which survived the treatment period showed a lower mortality during the observation time than those that were unprotected. The accumulative toxic effect of the substance must also be taken into consideration. It was often noted during this experimental series that the death of animals occurred in close connection with injection of cysteamine or with irradiation. This phenomenon will form the subject of a special investigation.

2. *Fraction dose 80 r, interval 3 days.* In accordance with the mathematical model, no acute death occurred in this series. The results will therefore be reported in a paper on chronic effects.

3. *Fraction dose 160 r, interval 1 day* (Table 2). In spite of the daily repeated irradiations, only a few unprotected animals could not tolerate higher accumulated doses, but the number of survivals was significantly higher compared with the number unprotected. Because of the relatively low number of cysteamine injections no accumulated toxic effect was observed.

4. *Fraction dose 160 r, interval 3 days* (Table 3). All animals survived after 960 r but some unprotected mice died after 1 280 r. The mortality increased con-

Table 3

Mortality after fraction dose 160 r — time interval 3 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
7.11.60	960	30	30							30	0
	960	*30*	*30*							*30*	*0*
	1 280	30	30		1	2				27	10.0
	1 280	*30*	*29*							*29*	*3.3*
	1 600	30	29	2	3	7	4	1		12	60.0
	1 600	*30*	*30*							*30*	*0*
	1 920	35	27	17	4	1				5	85.7
	1 920	*35*	*35*							*0*	*0*
22.8.61	1 600	30	29	9	7	2				11	63.4
	1 600	*30*	*29*	*2*	*2*	*3*	*2*		*1*	19	*36.7*
	1 920	29	23	13	6	3				1	96.5
	1 920	*30*	*29*	*3*	*6*	*4*			*1*	*15*	*50.0*
	2 240	30	6	5	1					0	100.0
	2 240	*30*	*24*	*1*	*4*	*1*				*18*	*40.0*
	2 560	30	2	1	1					0	100.0
	2 560	*30*	*12*	*4*	*3*					*5*	*83.3*
	2 880	30	0							0	100.0
	2 880	*30*	*3*	*2*	*1*					*0*	*100.0*
	3 200	30	0							0	100.0
	3 200	*30*	*1*	*1*						*0*	*100.0*
	3 520	30	0							0	100.0
	3 520	*30*	*2*	*1*						*1*	*96.7*
28.8.62	960	20	20							20	0
	1 280	20	20							*20*	*0*
	1 600	20	20				1			19	5.0
	1 920	20	15	8	3	2				2	90.0
	2 240	20	13	6			2		1	4	80.0

siderably after 1 600 r, and after 2 240 r all the animals died. The protective effect of cysteamine is apparent; the protected mice did not begin to die until after 1 600 r and some survived even after 2 560 r.

5. *Fraction dose 160 r, interval 7 days* (Table 4). All the irradiated, unprotected mice survived an accumulated dose of 2 240 r. After 3 200 r, about 50 % of the animals survived, but in the dose range of 3 840 r to 4 800 r only a few mice survived. All animals died after 5 760 r. A significant increase in the number

Table 4

Mortality after fraction dose 160 r — time interval 7 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
19.8.60	1 280	30	30							30	0
	1 280	*30*	*30*							*30*	*0*
	1 600	30	30							30	0
	1 600	*30*	*30*							*30*	*0*
	1 920	30	30							30	0
	1 920	*30*	*30*							*30*	*0*
	2 240	35	35							35	0
	2 240	*35*	*35*							*35*	*0*
17.5.61	2 880	28	23		1		2	2		18	35.7
	2 880	*27*	*25*							*25*	*7.4*
	3 200	29	27	1	6	1	2	1	1	15	48.3
	3 200	*29*	*21*	*2*		*1*	*2*	*1*		*15*	*48.3*
	3 520	29	15	1		2				12	58.6
	3 520	*29*	*28*					*1*		*27*	*6.9*
	3 840	28	5		1	1		1	1	1	96.5
	3 840	*28*	*14*		*2*			*1*	*1*	*10*	*64.3*
	4 160	28	8	4	2	1				1	96.5
	4 160	*29*	*5*						*1*	*4*	*84.0*
	4 480	27	4				1		1	3	92.5
	4 480	*30*	*17*	*1*	*1*			*2*		*13*	*56.6*
	4 800	28	2		1					1	96.5
	4 800	*29*	*14*		*3*	2	1			*8*	*72.3*
	5 760*	28	1	1						0	100.0
	5 920**	27	1	1						0	100.0

* This group should have been irradiated 40 times. The last mouse died on the day following the 36th irradiation.

** This group should have been irradiated 40 times. The last mouse died on the 5th day following the 37th irradiation.

of survivors was observed among the protected groups in the dose range of between 3 520 r and 4 800 r, in comparison with the unprotected groups. All the mice were dead after 5 920 r, however.

6. *Fraction dose 320 r, interval 1 day* (Table 5). All unprotected animals survived an accumulated dose of 640 r, but already at 960 r the majority had died, and all were dead after 1 280 r. A few protected mice died at 960 r; at 1 280 r some survived, and at 1 600 r all died.

Table 5

Mortality after fraction dose 320 r — time interval 1 day (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
13.6.62	640	30	30							30	0
	640	*30*	*30*		*1*					*29*	*3.3*
	960	30	30	4	7	9		1		9	70.0
	960	*30*	*29*	*1*						*28*	*6.7*
	1 280	30	30	1	28	1				0	100.0
	1 280	*30*	*29*		*12*	*9*	*1*			*7*	*76.8*
	1 600	35	32	5	27					0	100.0
	1 600	*35*	*24*	*3*	*20*	*1*				*0*	*100.0*

7. *Fraction dose 320 r, interval 3 days* (Table 6). Some unprotected mice died already at an accumulated dose of 960 r and the mortality was 100 % at doses higher than 1 280 r. Some of the protected animals died after 1 280 r but some survived at 1 920 r, indicating a good protection also in this case.

8. *Fraction dose 320 r, interval 7 days* (Table 7). A few deaths are recorded among the irradiated animals only at accumulated doses of 1 280 r and 1 600 r but at 1 920 and 2 240 r only a few survived. A very low mortality in the protected animals is, however, evident in this dose range, and at 3 200 r some survivors still remain. The protective effect of cysteamine in this group is obvious.

Mathematical model and Statistical analysis

According to the general opinion the recovery rate decreases in the time intervals between irradiations. This implies that the recovery rate during the first 24 hours after an irradiation should be greater than the recovery rate during the following days. Furthermore, the recovery rate is considered to be dependent on a previous irradiation dose (BLAIR 1961, SACHER 1958, STORER 1961).

Systematic deviations, indicating that a simpler model could fit, were evident when these concepts were applied to the present results. A mathematical model was therefore designed on the assumption that the absolute recovery was independent of any previous dose and independent of the time interval after the immediately preceding irradiation. The recovery rate per day was assumed to be constant for each animal. The effective dose received by an animal is then

$$ERD = AED - R \cdot T$$

where AED is the accumulated exposure dose, R the recovery rate in r/day and T is the number of recovery days, i. e. the time period between the first and last irradiation (Fig. 1). If $R \cdot T \geq AED$, ERD is defined as 0.

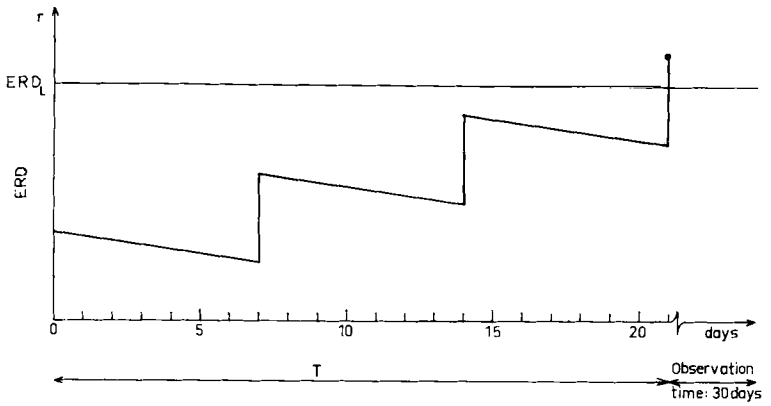

Fig. 1. ERD in r as a function of recovery time (T) for an animal whose ERD_L is exceeded in the last irradiation.

Table 6

Mortality after fraction dose 320 r — time interval 3 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
5.7.60	960	30	30		6	3				21	30.0
	960	*30*	*30*							*30*	*0.0*
	1 180	30	30	13	13	2	1		1	0	100.0
	1 280	*30*	*30*		*2*	*2*	*1*			*25*	*16.7*
	1 600	30	30	33	7					0	100.0
	1 600	*30*	*30*	*7*	*9*	*3*	*1*			*10*	*66.7*
	1 920	35	19	19						0	100.0
	1 920	*34*	*33*	*13*	*13*	*3*				*4*	*88.3*
7.4.61	960	30	30		2	5				23	23.3
	960	*30*	*30*							*30*	*0.0*
	1 280	30	30		24	2	3			1	96.6
	1 280	*30*	*30*		*3*		*1*	*2*	*1*	*23*	*23.3*
	1 600	30	28	27	1					0	100.0
	1 600	*30*	*30*	*12*	*10*	*1*			*1*	*6*	*80.0*
	1 920	30	9	9						0	100.0
	1 920	*20*	*11*	*5*	*6*					*0*	*100.0*
	2 240	30	3	3						0	100.0
	2 240	*20*	*10*	*5*	*4*	*1*				*0*	*100.0*
	2 560	30	0							0	100.0
	2 560	*29*	*2*	*2*						*0*	*100.0*

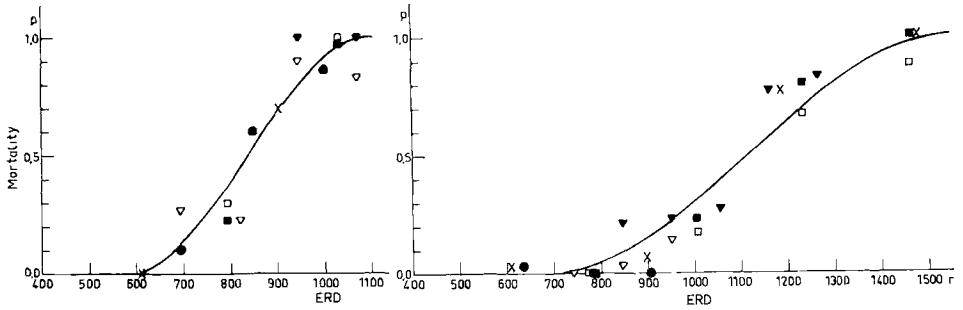

Fig. 2. Mortality as a function of ERD (series I): a) irradiated only; b) irradiated and protected.

● 160 r, 3 days, started 7.11.1960
× 320 r, 1 day, » 13.6.1960
□ 320 r, 3 days, » 5.7.1960
■ 320 r, 3 days, » 7.4.1961
▽ 320 r, 7 days, » 22.9.1960
▼ 320 r, 7 days, » 7.2.1961

Table 7

Mortality after fraction dose 320 r — time interval 7 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality %
		At beginning of irradiation	At end of irradiation	1–5	6–10	11–15	16–20	21–25	26–30		
22.9.60	1 280	30	30			4	2	2		22	26.7
	1 280	*30*	*30*							*30*	*0.0*
	1 600	30	30	1		3		2	1	23	23.4
	1 600	*30*	*30*							*30*	*0.0*
	1 920	30	27	10	10	4				3	90.0
	1 920	*30*	*29*							*29*	*3.3*
	2 240	35	26	13	5	1	1			6	82.8
	2 240	*35*	*35*		*2*	*2*	*1*			*30*	*14.3*
7.2.61	1 920	30	15	14	1					0	100.0
	1 920	*28*	*27*	*1*			*2*	*1*	*1*	*22*	*21.4*
	2 240	30	1	1						0	100.0
	2 240	*30*	*27*	*4*						*23*	*23.4*
	2 560	29	29							0	100.0
	2 560	*30*	*24*	*2*						*22*	*26.7*
	2 880	30	30							0	100.0
	2 880	*30*	*10*	*1*		*1*			*1*	*7*	*76.6*
	3 200	30	30							0	100.0
	3 200	*30*	*6*			*1*				*5*	*83.4*

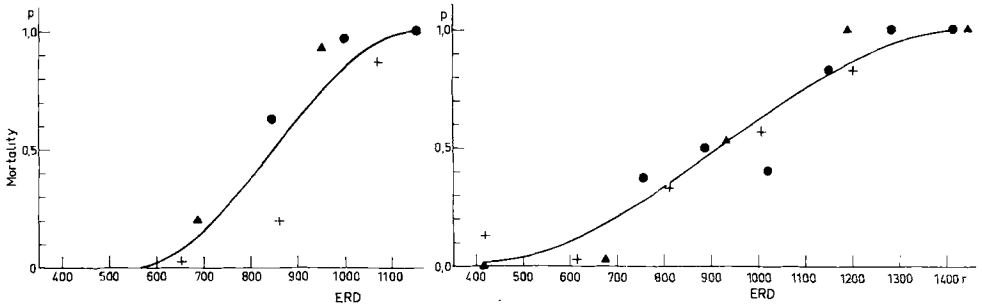

Fig. 3. Mortality as a function of ERD (series II): a) irradiated only; b) irradiated and protected.
+ 80 r, 1 day, started 13.2.1962
▲ 160 r, 1 day, » 17.1.1962
● 160 r, 3 days, » 22.8.1961

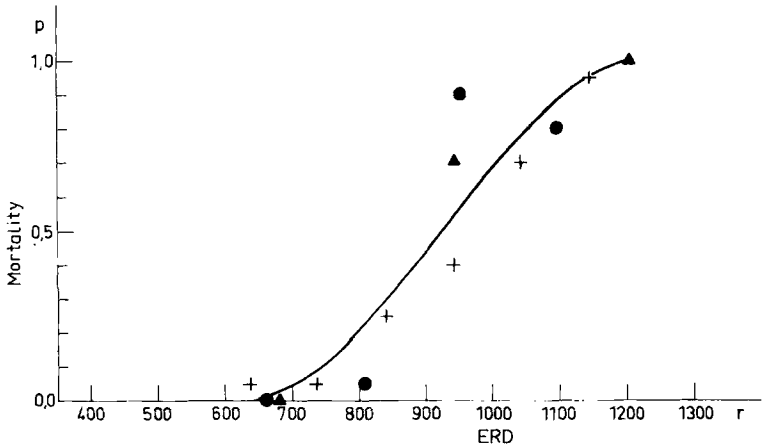

Fig. 4. Mortality as a function of ERD (series III); irradiated only.
+ 80 r, 1 day, started 28.8.1962
▲ 160 r, 1 day, » 28.8.1962
● 160 r, 3 days, » 28.8.1962

ERD is thus the accumulated dose corrected for such recovery as has occurred at a specific time (T).

If during the irradiation period the dose received by an animal exceeds a certain value ERD_L, death occurs, according to the model, before the end of the observation time, i. e. within 30 days after the last irradiation. It appears from Fig. 1 that if ERD_L is not exceeded at the last irradiation, the animal will survive.

The relationship between mortality and dose in our animal material may be expressed as a sine-square distribution, and this has therefore been assumed in our model for the distribution of ERD_L. The relation between mortality and ERD will form an S-shaped curve, which will only differ slightly from the normal distribution. When the sine-square distribution is applied, the observed mortality rate, p, is transformed according to

$$y = 2 \arcsin \sqrt{p} \text{ in which case}$$
$$y = a + b \text{ (ERD) } (a \text{ and } b \text{ are constants}).$$

After substitution of ERD

$$y = a + b\,(\mathrm{AED} - \mathrm{R}\cdot\mathrm{T}) = a + b\,(\mathrm{AED}) - c\cdot\mathrm{T} \text{ where } c = b\cdot\mathrm{R}.$$

The variable y can accept values between 0 and π.

By means of regression analysis a, b and c can be estimated, in which case an estimation of $\mathrm{R} = \frac{c}{b}$ can be obtained.

The statistical analysis gave the following equations for the five regression planes:

Ser I	Ir	$\hat{y} = -3.39 + 0.005929\cdot(\mathrm{AED}) - 0.1651\cdot\mathrm{T}$	R = 28
Ser I	Ir + P	$\hat{y} = -2.39 + 0.003536\cdot(\mathrm{AED}) - 0.1086\cdot\mathrm{T}$	R = 31
Ser II	Ir	$\hat{y} = -2.80 + 0.005148\cdot(\mathrm{AED}) - 0.1435\cdot\mathrm{T}$	R = 28
Ser II	Ir + P	$\hat{y} = -1.06 + 0.002876\cdot(\mathrm{AED}) - 0.0901\cdot\mathrm{T}$	R = 31
Ser III	Ir	$\hat{y} = -3.15 + 0.005098\cdot(\mathrm{AED}) - 0.1496\cdot\mathrm{T}$	R = 29

(Ir = irradiated, P = protected)

Series I includes experimental groups started not later than April 4th, 1961; series II was started between August 22nd, 1961 and February 13th, 1962, while series III was started on 28th of August, 1962.

Thus $\hat{y}$ is the expected value of y according to the model. From $\hat{y}$ the expected mortality can be calculated, which for $0 \leq \hat{y} \leq \pi$ is $0 \leq \hat{p} \leq 1$.

$\hat{y} < 0$ is regarded as $\hat{p} = 0$, and $\hat{y} > \pi$ as $\hat{p} = 1$.

The estimations of ERD can be obtained for each group of animals from AED, T and the estimation of R.

The curves in Figs 2, 3 and 4 give the relation between $\hat{p}$ and ERD. The observed mortality rates are marked in the figures.

The curves for Ir + P are extended over a greater range of ERD than the curves for Ir only, e. g. the standard deviation of $\mathrm{ERD_L}$ is greater for the protected than for the unprotected animals. The mean square deviation of the observed values, around the function that indicates the relationship between dose and mortality, should not be significantly greater than the theoretical variance determined by the binomial distribution. The mean square deviation around the lines in Figs 2, 3 and 4 is, however, significantly greater than the theoretical variance. This might depend on those age differences that arise due to the long duration of the experiment, even if the animals were of the same age at its inauguration. In addition, it should be pointed out that the various groups in series I and II were investigated at different times.

The most important control investigation of the validity of the model is an observation of systematic deviations, e. g. if points based on the same experimental conditions in Figs 2, 3 and 4 tend to show a systematic shift in relation to the curves. It is evident from Fig. 2a that some points show a deviation from the curve which is great in comparison with the expected deviation defined by the binomial distribution, although a systematic deviation is not observed in any group. Neither in Fig. 2b, where 'protection' has been added, can any systematic deviation be observed.

A systematic deviation is noted in Figs 3 and 4 which could indicate a higher recovery rate after a low dose, e. g. the points of the 80 r and 1 day-group show a lower mortality than might be expected. There is however no reason to conclude from the results that the recovery rate for the 160 r and 1 day-group should be greater than the recovery rate for the 160 r and 3 day-group.

Conclusions

The mathematical model was designed as a means of providing a statistical analysis of the acute lethal effect of fractionated irradiation. In the case of sufficiently low fraction dose, or long enough interval, i. e. within 30 days after

the last irradiation, no acute mortality is observed. When the duration of the experimental period is very extended, chronic effects will influence the results and a systematic deviation from the model is introduced, e. g. in the 160 r and 7 day-groups. Such a systematic deviation has, however, not been observed within 90 days from the first irradiation in the present study. No conclusion can be drawn regarding the validity of the model at shorter times since no experiment has been carried out with intervals shorter than 24 hours between the fraction doses.

The good agreement between the recovery rates of the irradiated as well as of the irradiated protected groups both in series I and II, in spite of the fact that the experiments were carried out at different times, is of great interest. Somewhat higher recovery rates have certainly been observed among the animal groups that received cysteamine but the difference must be regarded as insignificant.

The protective influence of cysteamine is apparent, and the recovery rates are practically the same in the protected and unprotected groups, which further supports the opinion that the results produced by cysteamine are initial, i. e. dose reduction effects.

Acknowledgement

The authors are indebted to C. Rönnbäck, S. Jäger, I. Andersson and R. von Knorring for their excellent technical assistance.

SUMMARY

Groups of mice were exposed to fraction doses at various time intervals in order to investigate the protective effect of cysteamine at sublethal levels of irradiation. Half the number of animals were given cysteamine before each irradiation. A simple mathematical model, which fitted the results regarding the short term lethal effects, was used. Cysteamine appears to act by producing a dose reduction effect and not an enhancement of the recovery.

ZUSAMMENFASSUNG

Gruppen von Mäusen wurden fraktionell bei verschiedenen Zeitabständen bestrahlt, um den Schutzeffekt von Cysteamin von nicht-tödlichen Strahlendosen zu beurteilen. Die Hälfte der Tiere erhielten Cysteamin vor jeder Bestrahlung. Ein einfaches mathematisches Modell wurde benutzt, das die Resultate der rasch tödlichen Effekte darstellte. Cysteamin scheint mehr eine Reduktion der Strahlendose zu bewirken als die Erholung von einer Strahlendose zu begünstigen.

RÉSUMÉ

Des groupes de souris ont été exposés à des doses fractionnées à intervalles de temps variées pour étudier l'effet protecteur de la cystéamine pour des taux d'irradiation subléthaux. La moitié de ces animaux ont reçu de la cystéamine avant chaque irradiation. Les auteurs se sont servis d'un modèle mathématique simple qui concordait avec les résultats concernant l'effet léthal à court terme. La cystéamine semble agir par un effet de réduction de dose et non en favorisant la guérison.

REFERENCES

BLAIR H. A.: Some properties of reparable and irreparable radiation injury. Univ. Rochester Report UR-602, 1961.

DOULL J., PLZAK V., and ROOT M.: The influence of exposure to low levels of gamma and fast neutron irradiation on the life span of mice. I. Chemical protection against chronic radiation injury. USAF Radiation Lab. Quarterly Progress Report No. 37 (1960), 53.

ELDJARN L., and PIHL A.: Mechanisms of protective and sensitizing action. *In:* Mechanisms in Radiobiology. Vol. 2, Chapter 4. Editors: M. Errera, and A. Forssberg. Academic Press, New York and London 1960.

LANGENDORFF H., und CATSCH A.: Untersuchungen über einen biologischen Strahlenschutz. XVI. Mitteilung. Über die Schutzwirksamheit des Cysteamin bei fraktionierter Ganzkörperbestrahlung von Mäusen. Strahlentherapie 101 (1956), 536.

— MELCHING H.-J., und LADNER H.-A.: Untersuchungen über einen biologischen Strahlenschutz. XXXII. Mitteilung. Zur Frage des biologischen Strahlenschutzes nach wiederholter Ganzkörperbestrahlung mit letal wirkenden Strahlendosen. Strahlentherapie 110 (1959), 34.

NOBLE J. F., ROOT M., and DOULL J.: The influence of exposure to low levels of gamma and fast neutron irradiation on the life span of mice. I. Chemical protection against chronic irradiation injury in mice. USAF Radiation Lab. Quarterly Progress Report No. 36 (1960), 107.

PATT H. M., MAYER S. H., STRAUBE R. L., and JACKSON E. M.: Radiation dose reduction by cysteine. J. cell. comp. Physiol. 42 (1953), 327.

RUGH R., and CLUGSTON H.: The time-intensity relations of whole-body acute x-irradiation and protection by β-mercaptoethylamine. Radiat. Res. 1 (1954), 437.

SACHER G. A.: Reparable and irreparable injury: A survey of the position in experiment and theory. *In:* Radiation biology and medicine. Chapter 12. Editor: W. D. Claus. Addison-Wesley Publishing Company, Reading, Mass. U. S. A. 1958.

STORER J. B.: Effect of dose size on rate of recovery from radiation damage in mice. Radiat. Res. 14 (1961), 206.