Increased Survival of Rats irradiated with X-Rays and treated with Parathyroid Extract

AN increase in the survival of rats irradiated with X-rays has been found when parathyroid extract is given either before or after the irradiation.

In our experiments, each rat received 200 U.S.P. units (2 ml.) of parathyroid extract (Eli Lilly) subcutaneously in the dorsothoracic region; control animals received an equal volume of normal saline. Both the parathyroid extract and the saline contained phenol as a preservative and were injected under sterile conditions. Males of a laboratory strain of hooded rats were used. They weighed 275–350 gm. at the beginning of each experiment. In one series, injections were given 12–18 hr. before irradiation. In a second series, animals were injected immediately after irradiation. All animals received 760 r. whole-body irradiation (measured in air) with 2,000 kVp. X-rays (1·5 m.amp.). This dose was given 65 cm. from the target at 400 r./min. No filters were used. Food and water were given ad libitum during the post-irradiation period.

When parathyroid extract was injected before or after irradiation, a difference was observed between the percentage surviving in the control and treated animals. By 20 days, this difference became highly significant (Table 1).

Table 1. EFFECT OF PARATHYROID EXTRACT ON THE NUMBER OF RATS SURVIVING 760 R. WHOLE-BODY IRRADIATION WITH X-RAYS

	Days after irradiation						Percentage surviving (30 days)
	0	10	15	20	25	30	
Pretreatment (12–18 hr. before irradiation)							
Saline (2 ml.)	119	117	94	74	68	63	52·9
Parathyroid extract (2 ml.)	119	118	109	102	98	97	81·5*
Post-treatment (immediately after irradiation)							
Saline (2 ml.)	56	50	23	14	12	12	21·4
Parathyroid extract (2 ml.)	54	51	41	38	37	36	66·7*

* $P < 0.001$ (chi-square)

When parathyroid extract was injected before irradiation, survival at 30 days irradiation was 52·9 per cent in the controls and 81·5 per cent in the treated animals (Table 1). When injections were given after irradiation, survival was 21·4 per cent in the controls and 66·7 per cent in the treated rats. This represents an increase in survival of 28·6 per cent and 45·3 per cent for rats injected with parathyroid extract before and after irradiation, respectively. These differences were highly significant ($P < 0.001$).

Between 30 and 60 days, the difference between the percentage surviving in the controls and treated animals was still evident, although slightly reduced. The percentage surviving in the controls was 51·3 and in the treated rats was 73·1, when treatment was administered before the irradiation. In rats injected after irradiation, the corresponding percentages at 60 days were 16·1 and 57·4.

It is not clear why fewer animals survived in the control group injected with saline immediately after irradiation (21·4 per cent) than in the controls injected before irradiation (52·9 per cent) (Table 1). However, a much greater proportion of gastrointestinal hæmorrhage occurred in the animals which died in the series injected after irradiation. This may have been the cause of the difference.

We conclude that the parathyroid extract used protects against radiation death. Experiments are in progress to determine whether this effect is a result of the activity of the hormone (that is, its ability to increase serum calcium[1]) or to some other property of the extract.

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Protective Action of Venoms containing Phosphatidase-A against Certain Bacterial Exotoxins

WE reported recently that a fraction of venom of the Australian tiger snake (Notechis scutatus scutatus), rich in hæmolysin, protects mice against both the dermonecrotic and lethal action of staphylococcal alpha toxin. Such an effect is observed when this fraction of the venom is injected either together with the toxin or separately[1].

Further work has shown that protection is not afforded by the crude venom of the tiger snake, nor by a fraction of the venom rich in neurotoxin but poor in hæmolysin. On the other hand, we have observed that the crude venom of the Australian black snake (Pseudechis porphyriacus), of the king brown snake (Pseudechis australis), and of the honey bee (Apis mellifera) gives the same order of protection against the lethal action of staphylococcal toxin in mice as does the hæmolysin-rich fraction of the venom of the tiger snake. The former three venoms, like that of the tiger snake, are strongly hæmolytic, all containing the enzyme phosphatidase-A (Doery, H. M. D., unpublished work). Unlike the venom of the tiger snake, however, they are not powerfully neurotoxic.

By toxoiding the hæmolysin-rich fraction of the venom of the tiger snake with 0·2 per cent formalin, the ratio of the resultant toxicity to the protective power was reduced from that of the untoxoided material. A notable protection against the lethal action of staphylococcal toxin was obtained with this toxoided fraction when it was administered up to 30 min. after the staphylococcal toxin.

Further, we have observed that both this toxoided fraction of tiger-snake venom and non-toxoided crude bee venom protect mice against intraperitoneal challenge with living staphylococci, the virulence of which was enhanced by Boake's[2] method (Table 1). This finding supports evidence that death following the intraperitoneal injection of mice with such living challenge is due to the production of alpha toxin (North, E. A., unpublished work).

It is known that the products of the action of phosphatidase-A on lecithin are a fatty acid and lysolecithin. Further, it was shown many years ago that soaps of certain long-chain fatty acids neutralize a number of bacterial toxins in vitro[3].

We have confirmed these findings as regards staphylococcal alpha toxin, tetanus toxin and diphtheria toxin using either sodium oleate or sodium linoleate. We have failed to demonstrate protection with the soap of the corresponding saturated acid, sodium stearate. In addition, we have observed that

Table 1. PROTECTION OF MICE AGAINST INTRAPERITONEAL CHALLENGE WITH LIVING VIRULENT STAPHYLOCOCCI BY A TOXOIDED TIGER SNAKE VENOM FRACTION AND CRUDE BEE VENOM

Test	Protective agent	Treatment when given in relation to challenge	Route	Day of death	Survivors after 7 days
1	Nil (controls)	—	—	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	4/20
	0·02 mgm. toxoided tiger snake venom fraction	75 min. before	Subcutaneous	1 1 1 2 3 4 5	13/20
	,, ,, ,,	45 min. after	Intravenous	1 1 1 1 1 1 1 1 1 1 3 3 7	7/20
2	Nil (controls)	—	—	1 1 1 1 1 1 1 1 1 1 1 1 1 3	2/15
	0·02 mgm. toxoided tiger snake venom fraction	95 min. before	Subcutaneous	1 2 2 4 4 5 5	8/15
	1/40 of one bee sting	100 min. before	Subcutaneous	1 1 1 1 2 4 4 7	7/15

All mice were challenged intraperitoneally with 1 ml. of a suspension of living coagulase-producing *Staphylococci* the virulence of which was enhanced by Boake's (ref. 2) clotting mixture.

protection against the lethal action of staphylococcal toxin in mice may be afforded by sodium oleate administered separately. Evidence has also been obtained that the hæmolysin-rich fraction of the venom of the tiger snake is antagonistic to the action of tetanus toxin in mice.

These observations suggest a possible defence mechanism against *in vivo* action of certain bacterial toxins. Phosphatidase-*A* [4] and lysophosphatides[5,6] have been reported to exist in animal tissues as such. Long-chain fatty acids may be liberated from phosphatides in cell envelopes as a response to the action of these toxins. The nature of the suggested interaction between the bacterial toxins and the fatty acids is not understood. This work is being reported in detail elsewhere.

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Comparison of the Effect of Ultra-violet and X-rays on the Capillaries of the Frog's Web

THE web between the toes of the frog is very suitable for the examination of the primary processes in the skin after irradiation with ultra-violet light, since the very thin corneal layer permits the entry of ultra-violet light of short wave-length. The transparency is measurable and makes possible the estimation of the absorption at different wave-lengths. To compare the effects of different wave-lengths, knowledge of the absorption coefficient at the site of biological action is necessary.

Transparency measurements were carried out in the range 280–600 mμ; below 280 mμ there was no transparency. The thickness of the layers (stratum corneum on each side, its layer of compensation, Malpighian layer and the dermis in the centre) was determined in histological cross-section. We were unable to detect a significant change in the absorption coefficient for the different layers, and therefore no influence of the histological structure was observed.

Fig. 1 shows average percentage of the applied radiation absorbed by a layer 1μ thick plotted against the depth of the layer. The diameter of the field measured was 2·4 mm. Ultra-violet irradiation was supplied by a high-efficiency monochromator with a high-pressure mercury lamp[1], *HBO* 2001. The radiant flux density was measured with a bolometer.

The reactions of the blood circulation to irradiation have been studied by Giersberg and Hanke[2] and by Bücker and Hanke[3]. Together with histological effects and changes in transparency with the changing water-content of the layers, the flow of blood was blocked even though the width of the vessels remained constant. The doses which produced this effect in 50 per cent of the animals were 10 watt sec. cm.$^{-2}$ (280 and 297 mμ) and 35 watt sec. cm.$^{-2}$ (313 mμ). 366 mμ had no effect. The absorption per layer 1μ thick was 0·3 per cent at 280 mμ (Fig. 1), 0·58 per cent at 297 mμ and 0·69 per cent at 313 mμ in the region of the capillaries on the irradiated side. The relative efficiency of the different wave-lengths
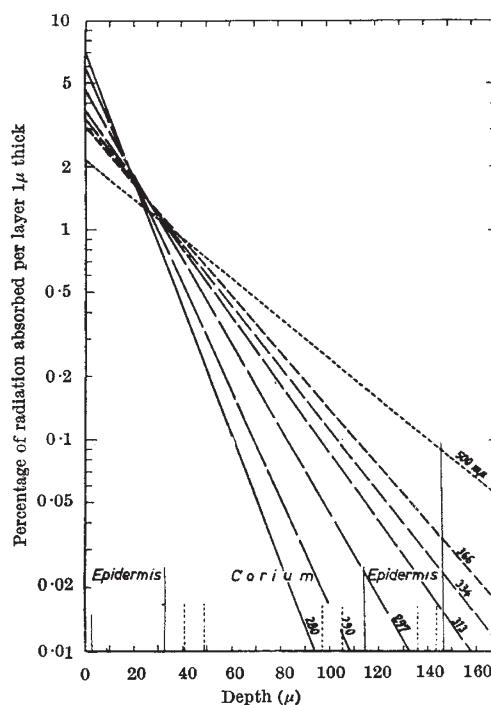

Fig. 1. Absorption in the web of the frog