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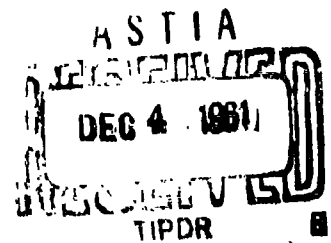
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SUBACUTE RADIATION DEATH IN CHEMICALLY
PROTECTED MONKEYS

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SCHOOL OF AEROSPACE MEDICINE
USAF AEROSPACE MEDICAL CENTER (ATC)
BROOKS AIR FORCE BASE, TEXAS

SUBACUTE RADIATION DEATH IN CHEMICALLY PROTECTED MONKEYS

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SUBACUTE RADIATION DEATH IN CHEMICALLY PROTECTED MONKEYS

A new mode of death caused by radiation has been characterized in monkeys. Called *subacute* death, it occurs in animals that would not ordinarily survive 30 days after a supralethal dose of x-rays but do so because of protection conferred by chemical treatment prior to irradiation. The syndrome includes lymphocytopenia, usually accompanied by diarrhea. Histologically, atrophy of lymphoid tissue, along with a relatively normal bone marrow, is typically found. The spectrum of other lesions found at death is also different from that found after acute radiation death.

The 30-day period is commonly used to separate acute radiation deaths from deaths due to the late complications of irradiation. Irradiated animals surviving the 30-day period will usually continue to live indefinitely. In the course of experiments on chemical protection against radiation injury in the monkey (5), a significant number of monkeys were observed to survive 30 days, appear clinically normal, but then become ill and die as late as four months after irradiation. Animals dying somewhat later than those which experienced the typical acute radiation death were found to have a different spectrum of pathologic lesions at autopsy. This report is concerned with a comparison of the incidence of lesions in (1) the group of protected animals dying a subacute death, (2) in the protected animals dying within 30 days, and (3) in unprotected irradiated monkeys dying an acute death.

MATERIALS AND METHODS

The monkeys used in these experiments were immature *Macaca mulatta* monkeys which had been cared for as previously described (4, 12).

X-irradiations were accomplished with a Picker x-ray machine at 250 kvp, 18 ma. with

1 mm. aluminum and 0.25 mm. copper added filtration. The dose rate was 19 to 20 r a minute; the animal exposure cage was rotated at 15 r.p.m. Totals of 525, 588, 672, and 756 rads were given to various monkeys.

Protective agents included S-(2-aminoethyl)thiuronium (AET), cysteine as the hydrochloride monohydrate, pentobarbital sodium, and chlorpromazine. These drugs were given separately or in various combinations, at different dose levels, and by parenteral and oral modes of administration. The methods of preparation, combination, and administration have been reported (5, 6). Antibiotics were sometimes used postirradiation. The animals were observed until death.

The particular form of protection and the dose of radiation were not significantly correlated to the results given here. All statements apply to all protected animals in the aggregate. Some recent protective combinations (AET-cysteine, given orally plus a sedative, given intraperitoneally) provide better protection against both acute and subacute death.

Autopsies were performed shortly after the animals died. Most, but not all, animals studied were autopsied. Tissues were fixed in 10 percent buffered formalin, dehydrated, and embedded in paraffin, in the routine manner. Histologic sections were cut at 4 to 6 μ thickness and stained with hematoxylin and eosin. Special stains were occasionally utilized.

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This work was accomplished at the Radiobiological Laboratory of the University of Texas and the United States Air Force, Austin, Tex.

TABLE I

Incidence of death at various time intervals

Days postirradiation	Control (10)*	Protected (83)
0 - 30	88% (14)	60 % (50)
30 - 40	0 (0)	4 % (3)
40 - 110	6% (1)	18 % (15)
Over 110	0 (0)	2 % (2)
Living	6% (1)	16 % (13)

*Number of animals given in parentheses.

TABLE II

Clinical findings in 15 protected animals dying subacute death

Symptom	Number of animals
Diarrhea	12
Inactivity	6
Poor appetite	3
Eosinophilia	6
Lymphocytopenia	14

TABLE III

Incidence of lesions at autopsy

Lesion	Controls, acute death (12)*	Protected, acute death (47)	Protected, subacute death (15)
	Percent		
Bone marrow hypocellularity			
Severe	84	79	7
Mild	8	13	40
None	8	8	53
Lymphoid atrophy	100	100	67
Hemorrhagic phenomena	100	85	20
Meningitis or ependymitis	8	2	40
Colitis			
Severe	33	45	20
Slight	42	15	33
Inflammation or ulceration of superficial tissues	25	30	0
Morphologic lesion of bacteremia	33	23	0
Abscesses (large)	0	0	13
Gastric lesions	8	15	20
Miscellaneous acute lesions	0	15	47

*Number of animals given in parentheses.

RESULTS

The time distribution of deaths is shown in table I. Deaths that took place within 30 days after irradiation were considered acute. Within the 30-day period the greater number of deaths occurred between 10 and 20 days. One unprotected animal (525 rads) lived 69 days after irradiation. In the protected group, a much larger percentage survived the 30-day period, but more than half of this group died by the 110th day. A percentage greater than that of the control group continued to survive indefinitely.

The animals which died a subacute death had a variety of clinical findings prior to death. See table II. Lymphocytopenia was the most consistent finding, and diarrhea was very common. Inactivity, anorexia, and eosinophilia were also observed.

A variety of lesions was found at autopsy. The incidence of the various lesions is presented in table III. In general, the distribution of lesions was the same in acute death, whether the animals were protected or not; but a different distribution was observed in protected animals which died a subacute death. A few

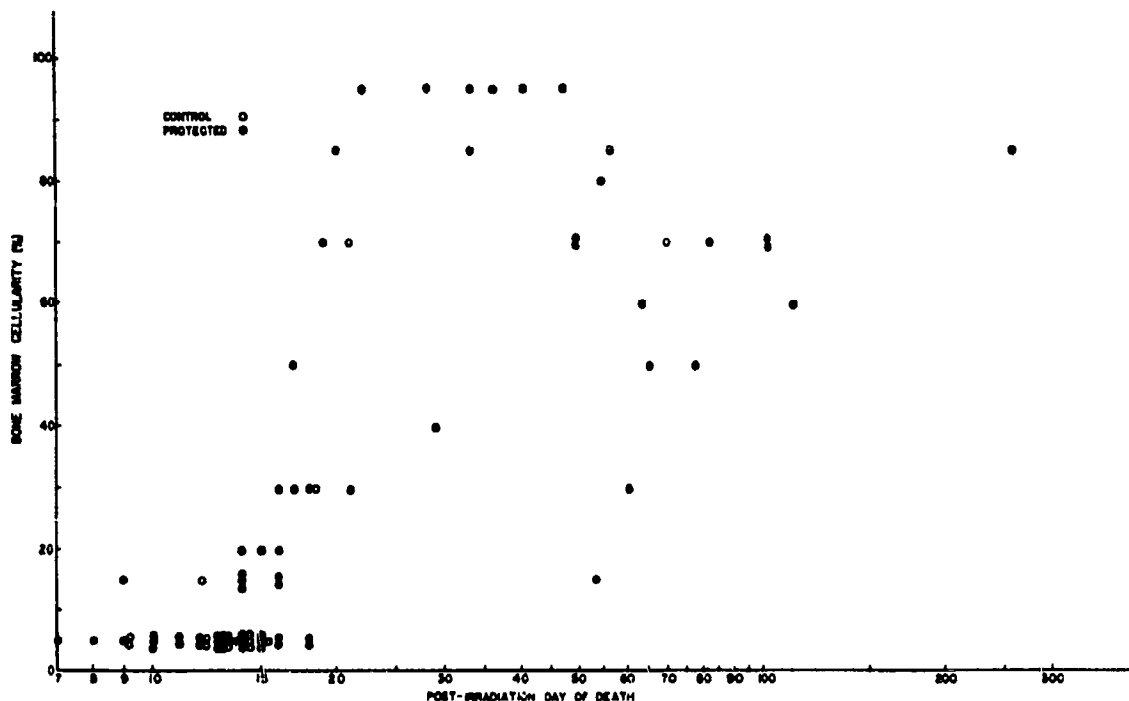


FIGURE 1

Approximate bone marrow cellularity as a function of time after death.

unprotected animals from other experiments, which died in the time interval of subacute death, seem to have had a lesion distribution similar to that of the protected monkeys dying a subacute death. The number of animals of this type available for comparison is too small to permit drawing any conclusions.

The bone marrow in the animals dying an acute death was commonly severely atrophic, with some regeneration being present in animals dying after 18 to 20 days. The bone marrow was normal or only mildly atrophic in animals dying a subacute death. Bone marrow cellularity as a function of time after death is presented in figure 1.

Lymphoid tissues, in general, are atrophic in both acute and subacute deaths. The degree of atrophy may vary, but it is generally quite obvious. Even the tissues which had some lymphoid regeneration were not completely normal and lymphoid follicles were rarely seen.

This is probably the histologic counterpart of the peripheral lymphocytopenia seen in animals dying a subacute death.

Hemorrhagic phenomena of significant degree were far more common in the acute deaths than in the subacute deaths, probably because of the differences in platelet count in animals with and without bone marrow. Meningitis and endymitis were seen several times in animals dying a subacute death but only rarely in those dying acute deaths. The incidence of colitis probably does not vary significantly between groups. Superficial inflammatory lesions were common in acute deaths but not in subacute deaths. Lesions of bacteremia, such as microabscesses and bacterial colonies, are commonly seen in acute deaths but not in the subacute deaths. Large abscesses of the type which might be surgically drained have been seen in subacute deaths, however. A variety of miscellaneous acute lesions—including

vasculitis, duodenal ulcer, and pyelonephritis—are seen in subacute deaths. The higher incidence of gastric lesions, generally of a relatively minor nature, in the protected animals may be a reflection of the irritative properties of some of the protective agents.

DISCUSSION

Chemical protection of the monkey may successfully offset the acute effects of lethal doses of ionizing radiation. The use of chemical agents in our experiments seems to have uncovered another mode of death which occurs at a later time. We have used the term *subacute* to describe the later death, because of the time interval. This mode of death commonly occurs after marrow regeneration is nearly or entirely complete. Lymphoid atrophy is usually present, however, and the peripheral blood reveals lymphocytopenia. Such a death could, therefore, be referred to as *lymphoid* death to distinguish it from the bone marrow death of the animals dying acutely.

Studies in smaller laboratory animals have demonstrated that many chemicals protect the bone marrow but not the lymphoid tissues (2, 3, 7). The data herein fail to support chemical protection of the bone marrow in the monkey, but a serial examination of marrow cellularity of surviving animals might well have shown earlier marrow regeneration. There seems to be little doubt that chemical treatment allows the animals to survive long

enough for the bone marrow to be restored to a considerable extent. The lymphoid tissues seem to require a longer time for complete regeneration. Preliminary studies indicate some derangements in serum proteins. A loss of albumin, as shown by a low albumin/globulin ratio, is the usual finding in the sickening animal, but further information will be required before a definite statement can be made.

Monkeys exhibit the modes of radiation death usually reported in rodents (9), and the histopathology has been described (1, 10, 11). In protected rats surviving 30 days after a supralethal dose of gamma radiation, no pattern comparable to that of subacute death has been observed (8).

SUMMARY

A subacute death in irradiated, protected monkeys has been characterized in terms of the relative incidence of pathologic lesions, as compared to acute deaths in protected and nonprotected animals. Clinically, the symptoms most often noted are lymphocytopenia, diarrhea, and general debilitation. Histopathologically, the lesions most often seen are lymphoid atrophy, with a nearly normal bone marrow, and a different spectrum of other lesions. There is no evidence that chemical radioprotectants prevent bone marrow damage in monkeys.

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