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**ALTERATION OF POSTIRRADIATION
HYPOTENSION AND INCAPACITATION
IN THE MONKEY BY ADMINISTRATION
OF VASOPRESSOR DRUGS**

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
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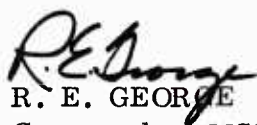
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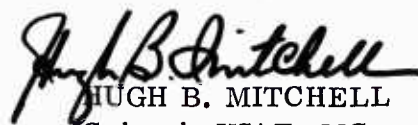
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ALTERATION OF POSTIRRADIATION HYPOTENSION AND INCAPACITATION
IN THE MONKEY BY ADMINISTRATION OF VASOPRESSOR DRUGS

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FOREWORD

(Nontechnical summary)

A rapid decrease in blood pressure has been observed in monkeys immediately after they received supralethal doses of ionizing radiation. This initial decrease in blood pressure is frequently followed by a temporary return to near normal pressure and a more gradual second decrease ending in death of the animal. The blood pressure changes in supralethally irradiated monkeys appear to bear some relationship to the ability of the animals to perform useful work. The objective of this study was to reduce or eliminate the early transient decrease in blood pressure by the use of drugs. The effect of norepinephrine, angiotensin, ephedrine, and amphetamine on both the early decrease in blood pressure and the incapacitation observed in monkeys following a 4-krad pulsed dose of mixed gamma-neutron radiation was investigated.

Seven monkeys served as controls and received only the 4-krad dose of radiation. As expected, severe early postirradiation hypotension and accompanying incapacitation occurred.

Norepinephrine or angiotensin was administered to five other monkeys by intravenous infusion from 5 minutes prior to irradiation until death, except that the infusion was temporarily interrupted several times after the animals had received the 4-krad dose. The increased blood pressure resulting from preirradiation drug administration did not prevent the characteristic early postirradiation fall in mean blood pressure, but severity of the resulting hypotension was reduced. Cessation of drug infusion after irradiation caused a rapid drop in blood pressure

with the animals becoming incapacitated (loss of consciousness) when mean blood pressure fell below a critical level (approximately 50 mm Hg). After drug infusion was resumed, consciousness returned as the blood pressure rose above the critical level. This sequence was repeated several times before the animal failed to respond to drug administration and died abruptly.

Five other monkeys were given a single intravenous injection of ephedrine or amphetamine 1 hour before irradiation; these animals received no further treatment. Ephedrine administration appeared to be as effective at maintaining satisfactory postirradiation blood pressure as norepinephrine and angiotensin.

ABSTRACT

The effect of vasopressor drugs on the early hypotension and incapacitation observed in monkeys following a 4-krad pulsed dose of mixed gamma-neutron radiation was investigated. Seven monkeys received only the 4-krad dose of radiation and served as controls. Norepinephrine or angiotensin was administered to five other monkeys by intravenous infusion from 5 minutes prior to irradiation until death, except that infusion was temporarily interrupted several times after irradiation of the animals. Blood pressure was continuously monitored in all animals. Drug-induced blood pressure elevation prior to irradiation did not prevent the characteristic early postirradiation fall in mean blood pressure, but severity of the resulting hypotension was reduced. Cessation of drug infusion after irradiation resulted in a rapid drop in blood pressure with the animal becoming incapacitated (loss of consciousness) when mean blood pressure fell below a critical level of about 50 mm Hg. After drug infusion was resumed, consciousness returned as the blood pressure rose above the critical level. This sequence was repeated several times before the animal failed to respond to drug administration and died abruptly in a hypotensive state. Five other monkeys were given a single intravenous injection of ephedrine or amphetamine 1 hour before irradiation; these animals received no further treatment. Ephedrine administration appeared to be as effective at maintaining satisfactory postirradiation blood pressure as norepinephrine and angiotensin.

I. INTRODUCTION

Early transient hypotension, performance decrement, and incapacitation in monkeys (Macaca mulatta) after supralethal doses of radiation have been described.^{1, 5, 7, 9} Radiation-induced incapacitation has been shown to parallel hypotension in monkeys and a causal relationship has been suggested.²

In this study the effect of several vasopressor drugs on early hypotension and incapacitation in monkeys after mixed gamma-neutron irradiation was investigated.

II. MATERIALS AND METHODS

Male and female monkeys (Macaca mulatta) weighing 3-4.5 kg were used. The conditioning and maintenance of these animals have been previously described.⁸

One week before the animals were irradiated, a catheter,* filled with heparinized saline, was surgically inserted into the abdominal aorta of each monkey via the femoral artery. A similar catheter was placed in the femoral vein. These catheters were used in measuring blood pressure and administering drugs, respectively. The arterial pressure at each observation time was expressed as the mean pressure (half the sum of the values for the systolic and diastolic pressures). Following surgery the monkeys were placed in primate restraining chairs[†] where they remained throughout the experiment.

Generally, one drug-treated and one control monkey were simultaneously irradiated (Figure 1), however, five of the monkeys were individually irradiated. All monkeys were dorsal-ventrally exposed to mixed gamma-neutron radiation delivered

* Vinyl tubing No. 6179 (i.d. - 0.044 inches; o.d. - 0.065 inches), Becton, Dickinson and Company, Rutherford, New Jersey

† Model #1206, Foringer and Company, Inc., Rockville, Maryland

as a single pulse of approximately 50 milliseconds duration. The resulting midline tissue dose was 4 krad. The radiation environment⁶ and dosimetry methods³ have been previously reported.

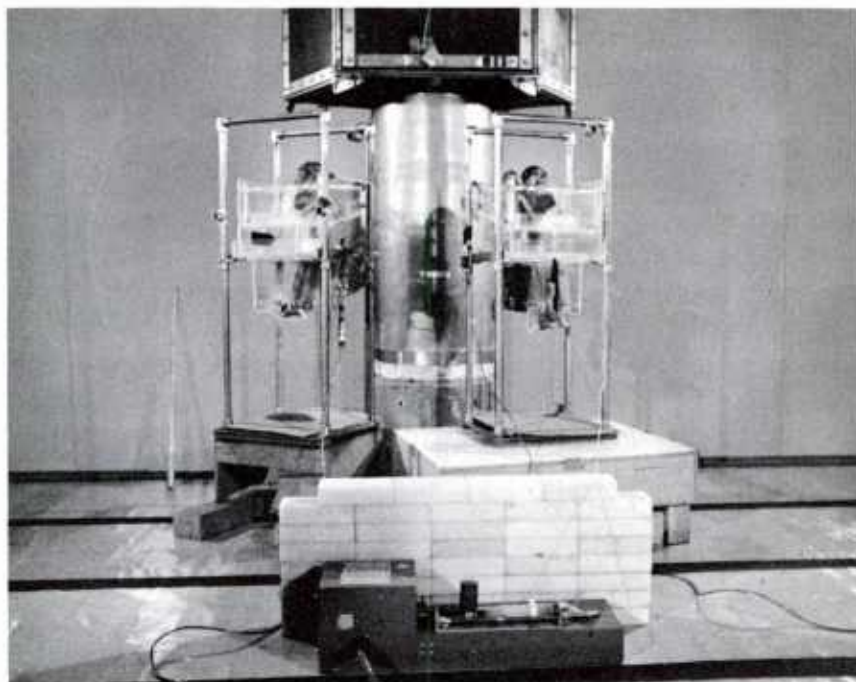


Figure 1. Monkey exposure array

Animals were judged incapacitated when they lost consciousness.

Seven monkeys received only the 4-krad dose of radiation and served as controls for evaluating the effectiveness of vasopressor drug administration. The vasopressor drug norepinephrine or angiotensin was administered to five monkeys using a constant rate infusion pump. Infusion commenced approximately 5 minutes prior to exposure, so that the monkeys were hypertensive when irradiated; mean blood pressure was at least 30 percent higher than the pretreatment value of approximately 95 mm Hg. After irradiation the flow rate of the infusate was sometimes altered in an effort to maintain

the predrug, preirradiation blood pressure of the monkeys. Drug infusion was continued until death except that the infusion was temporarily interrupted several times after the animals were irradiated.

Ephedrine sulfate or amphetamine hydrochloride was administered as a single intravenous injection to an additional five monkeys approximately 1 hour before the animals were irradiated. Blood pressure was monitored until death, but no additional attempt was made to maintain the blood pressure near preirradiation values in these monkeys.

III. RESULTS

Six of the seven control monkeys had a rapid, immediate postirradiation drop in blood pressure and showed clinical signs of incapacitation (Figure 2a). The mean blood pressure of the monkey which did not become incapacitated followed the same pattern seen with the other six except that it did not fall below 50 mm of Hg.

In four monkeys infused with norepinephrine and one infused with angiotensin, the characteristic fall in mean blood pressure after irradiation was not prevented despite preirradiation elevation to as high as 160 mm of Hg. However, the severity of postirradiation hypotension was reduced. Figure 2b-f illustrates the first 15-minute postirradiation blood pressure response of the drug-infused animals and of the control animals that were irradiated at the same time. None of the four animals infused with norepinephrine displayed any loss of consciousness during the first 15 minutes postirradiation when the drug was being continuously administered. After 15 minutes the infusion of norepinephrine was stopped in all animals and the blood pressure allowed to fall until the animal became unconscious. Infusion of the drug was then reinstituted

and consciousness returned. After this sequence was repeated several times, the blood pressure no longer responded to drug infusion and a progressive irreversible hypotension resulted which terminated in death. In one monkey, the infusion of

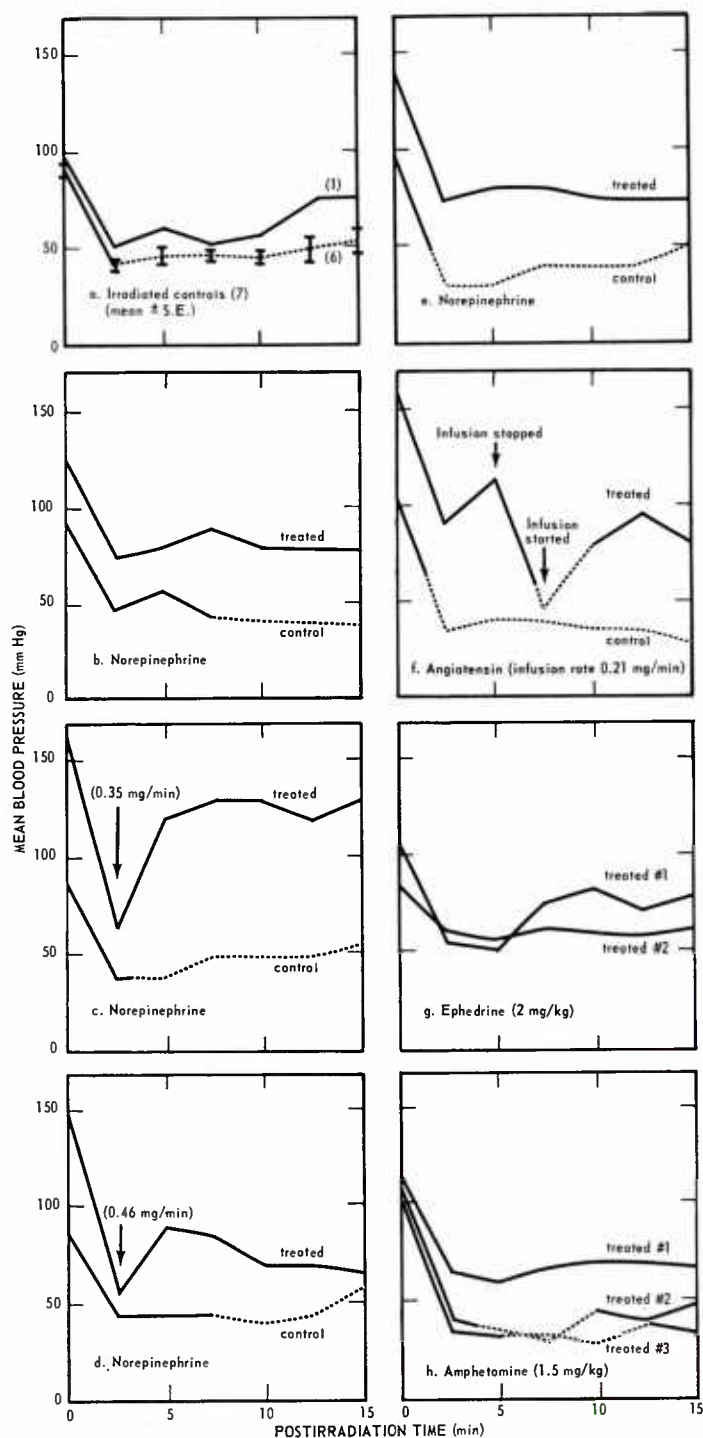


Figure 2. Mean blood pressure of monkeys after a 4-krad pulsed dose of mixed gamma-neutron radiation. Norepinephrine infusion rate was 0.23 mg/min except where shown (c and d). Dashed lines indicate incapacitation.

angiotensin was stopped at 5 minutes postirradiation (Figure 2f). By 7-1/2 minutes postirradiation, the mean blood pressure had fallen below 50 mm of Hg and the animal was unconscious. At this time, infusion of angiotensin was reinstituted, the blood pressure rose, and the animal regained consciousness 10 minutes after irradiation.

The survival time of the monkeys infused with norepinephrine (313 ± 16 min) was significantly greater ($P < .001$) than that of control animals (77 ± 16 min).

Two monkeys were treated with ephedrine and did not show signs of incapacitation. Although the mean blood pressure at the time of irradiation was only slightly higher than control values, the hypotension after irradiation was not as severe (Figure 2g).

Three monkeys were treated with amphetamine. Two became unconscious (incapacitated) after irradiation (Figure 2h). The mean blood pressure of the third remained above 50 mm Hg and it did not show signs of incapacitation.

Clinically, the ephedrine- and amphetamine-treated monkeys appeared more alert and active before and after irradiation than control monkeys. When the amphetamine-treated animals became incapacitated, the period of incapacitation was brief and the animals appeared more alert and active after recovery than did the control monkeys.

IV. DISCUSSION

The blood pressure in untreated monkeys after a 4-krad pulsed dose of mixed gamma-neutron radiation behaved in a fashion similar to that reported for other modes of irradiation.^{1,2} Approximately 30 seconds after irradiation mean blood pressure began to deteriorate rapidly reaching 50 mm Hg or less in about 2.5 to 5 minutes.

It was during or immediately following this rapid drop in blood pressure that six of the seven control monkeys became comatose and were incapacitated. These monkeys remained unconscious for 10 to 15 minutes after which their condition temporarily improved or death promptly ensued. When postirradiation mean blood pressure was maintained above 50 mm Hg by norepinephrine, angiotensin, or ephedrine administration, no clinical signs of incapacitation occurred. In general, as long as the pressure remained above 50 mm Hg, the animals were alert and active, when the blood pressure fell below this level, the animals lapsed into unconsciousness. Thus, there appears to be a critical mean blood pressure (approximately 50 mm Hg) which must be exceeded if incapacitation is to be avoided. The fact that drug-treated animals appeared alert and active after irradiation does not necessarily mean that they could perform a learned task during this period.

The dependence of alertness on blood pressure was demonstrated by interrupting drug infusion at various times after irradiation. The monkey treated with angiotensin did not appear incapacitated until approximately 7-1/2 minutes postirradiation when the mean blood pressure had fallen to about 50 mm Hg (2-1/2 minutes after infusion had been stopped). The monkey regained consciousness, however, after angiotensin infusion was reinstituted and mean blood pressure rose above 50 mm Hg. Cessation of norepinephrine infusion after irradiation also resulted in a rapid fall in blood pressure and incapacitation which was ameliorated by again infusing norepinephrine. Eventually, however, all animals failed to respond to treatment and abruptly died.

The survival time of irradiated monkeys was also extended significantly by infusion of norepinephrine.

The hypotension immediately following supralethal pulsed doses of radiation resembles neurogenic shock seen after severe brain damage resulting from physical trauma.⁴ Neurogenic shock is characterized by a loss of vasomotor tone, pooling of blood in the extremities, a rapid fall in blood pressure, ischemia to the brain, and a loss of consciousness by the subject. Several of these clinical symptoms were observed in the monkeys of this study. Furthermore, several drugs used in the treatment of neurogenic shock were effective for some time in the irradiated monkeys. Although cerebral blood flow was not measured in the current study, it has been reported that in primates, a precipitous fall in cerebral flow immediately following supralethal irradiation occurs which parallels systemic hypotension.²

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13. ABSTRACT The effect of vasopressor drugs on the early hypotension and incapacitation observed in monkeys following a 4-krad pulsed dose of mixed gamma-neutron radiation was investigated. Seven monkeys received only the 4-krad dose of radiation and served as controls. Norepinephrine or angiotensin was administered to five other monkeys by intravenous infusion from 5 minutes prior to irradiation until death, except that infusion was temporarily interrupted several times after irradiation of the animals. Blood pressure was continuously monitored in all animals. Drug-induced blood pressure elevation prior to irradiation did not prevent the characteristic early postirradiation fall in mean blood pressure, but severity of the resulting hypotension was reduced. Cessation of drug infusion after irradiation resulted in a rapid drop in blood pressure with the animal becoming incapacitated (loss of consciousness) when mean blood pressure fell below a critical level of about 50 mm Hg. After drug infusion was resumed, consciousness returned as the blood pressure rose above the critical level. This sequence was repeated several times before the animal failed to respond to drug administration and died abruptly in a hypotensive state. Five other monkeys were given a single intravenous injection of ephedrine or amphetamine 1 hour before irradiation; these animals received no further treatment. Ephedrine administration appeared to be as effective at maintaining satisfactory postirradiation blood pressure as norepinephrine and angiotensin.			