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NOREPINEPHRINE EFFECTS ON EARLY POSTIRRADIATION PERFORMANCE DECREMENT IN THE MONKEY

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Bethesda, Maryland

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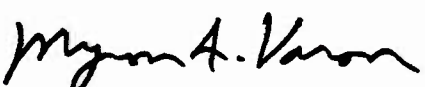

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FOREWORD
(Nontechnical summary)

Four thousand rads of pulsed mixed gamma-neutron radiation usually cause monkeys to be temporarily unable to perform a learned task. This early transient incapacitation is accompanied by a severe drop in blood pressure. The currently reported experiment was designed to determine whether the prevention of low blood pressure by intravenous infusion of norepinephrine, a vasoconstrictor, would have a beneficial effect on the postirradiation performance of monkeys.

Twenty male monkeys were trained to perform a task which consisted of moving a lever associated with a stimulus light. Each of the animals was then given 4000 rads of mixed gamma-neutron radiation and its blood pressure and ability to perform the learned task were measured. Ten of the monkeys were treated with a postirradiation intravenous infusion of norepinephrine to prevent the usual severe drop in blood pressure; the other ten trained monkeys were used as controls and given a postirradiation infusion of isotonic saline.

Postirradiation performance of the animals was frequently below satisfactory levels during periods of severe hypotension. However, there were also numerous occasions when the blood pressure was considered adequate (at least 60 percent of preirradiation values) but performance was quite poor. Apparently inadequate blood pressure is a limiting factor in the capacity to perform, but adequate blood pressure is not a guaranty of good performance.

Norepinephrine effectively maintained the blood pressure of eight of ten monkeys. When the average blood pressure of the treated animals was compared with the

average of the ten saline-treated controls, there was a significant difference. However, there was no statistically significant difference between the average performance of these two groups.

ABSTRACT

Monkeys, trained to perform a discrete trial, cued avoidance task, were used to measure the effectiveness of intravenously infused norepinephrine in preventing the hypotension and performance decrement which usually follows 3000- to 30,000-rad doses of radiation. After a 4000-rad dose of mixed gamma-neutron radiation, 10 animals were infused with norepinephrine at a rate designed to maintain mean arterial blood pressure at approximately 100 mm Hg; for comparison 10 control animals were infused with only isotonic saline after similar irradiation. Norepinephrine, although generally adequate for maintaining blood pressure, did not consistently improve performance during the first 30 minutes postirradiation.

I. INTRODUCTION

Following supralethal doses of ionizing radiation, in the range of 3000 - 30,000 rads, monkeys usually experience a partial or complete inability to perform a learned task. This early incapacitation is characteristically transient and is followed by a temporary recovery to normal or near normal levels of performance; this, in turn, is followed by severe performance decrement and death.[7-9]

The period of early transient incapacitation (ETI) is preceded or accompanied by hypotension, and a causal relationship has been suggested.[1] An earlier study of untrained monkeys whose postirradiation blood pressures were maintained by norepinephrine or other pressor drugs showed that as long as the arterial pressure remained above a critical level of approximately 60 percent of preirradiation pressure, the monkeys remained conscious and appeared alert.[5] However, no measurements were made of the monkeys' ability to perform a learned task. The present study evaluates the effect of norepinephrine on the ability of monkeys to perform a learned task after 4000 rads of mixed gamma-neutron radiation.

II. METHODS AND MATERIALS

Twenty male Macaca mulatta, 2 to 3 years old and weighing 3 to 4 kg, were used. Each animal had femoral arterial and venous catheters surgically implanted 3 days before irradiation.

Each monkey was trained to perform a discrete trial, cued avoidance task which consisted of moving one of two levers, each associated with a single stimulus light. A trial consisted of a stimulus light being lit for 5 seconds, accompanied by a warning tone during the 1st second. If the animal operated the lever associated with the light,

the light was extinguished and the trial ended. If the animal failed to move the correct lever within 5 seconds, it received a 1/2-second electrical shock. Ten seconds elapsed between the start of one trial and the start of the next. Light cues were presented in random order an equal number of times within blocks of 100 trials except that no lever was cued correct consecutively for more than three trials. One hundred trial sessions were separated by a 5-minute rest period.

Each animal was trained until it had performed 2000 trials (400 trials per day) at the criterion level of 90 percent or more correct. Total training time averaged 21 days.

One day before irradiation the monkey was tested for 2 hours to establish a base line, and on the day of irradiation each animal was positioned in the exposure room and given a 100-trial test to insure that a criterion level of performance was maintained. All animals were tested for a maximum of 120 minutes following irradiation.

Each animal received a 4000 ± 400-rad midline tissue dose of mixed gamma-neutron radiation delivered as a short duration pulse (approximately 25 milliseconds, pulse width at half maximum height).

Arterial blood pressure was monitored* and at the moment of irradiation an infusion pump† was turned on. In 10 of the animals the rate of infusion was automatically controlled‡ to infuse norepinephrine§ (1 mg/ml) at a linearly increasing rate with decreasing blood pressure from 100 mm Hg to 50 mm Hg; maximum infusion rate (1.23 ml/min) occurred when the arterial pressure was 50 mm Hg or less. The norepinephrine infusion was maintained, as needed, until the end of the testing period.

* Pressure transducer, Type P23Db, Statham Laboratories Inc., Hato Rey, Puerto Rico
† Infusion pump, Harvard Apparatus Company, Millis, Massachusetts
‡ Servo Control Amplifier, Harvard Apparatus Company, Millis, Massachusetts
§ Levophed brand of levarterenol, Winthrop Laboratories, New York, N. Y.

The 10 control animals were infused with isotonic saline at a rate of 1.23 ml/min for the 1st minute following irradiation, nine-tenths of this rate for the 2nd minute, eight-tenths for the 3rd minute, and so on for a total of about 7 ml of saline.

Mean arterial blood pressure (MAP) was calculated as diastolic pressure plus one-third of pulse pressure. The "critical level" of MAP is defined as 60 percent of preirradiation pressure. Severe performance decrement is defined here as less than 50 percent correct responses in a given block of 100 trials.

Student's "t" test was used to test the significance of group mean data; p values less than 0.05 were considered significant.

III. RESULTS

Typical of monkeys receiving a 4000-rad dose of radiation, severe hypotension generally occurred very soon after irradiation in the saline-treated animals (Figures 1 and 2). In most instances the hypotension was accompanied or followed by a period of

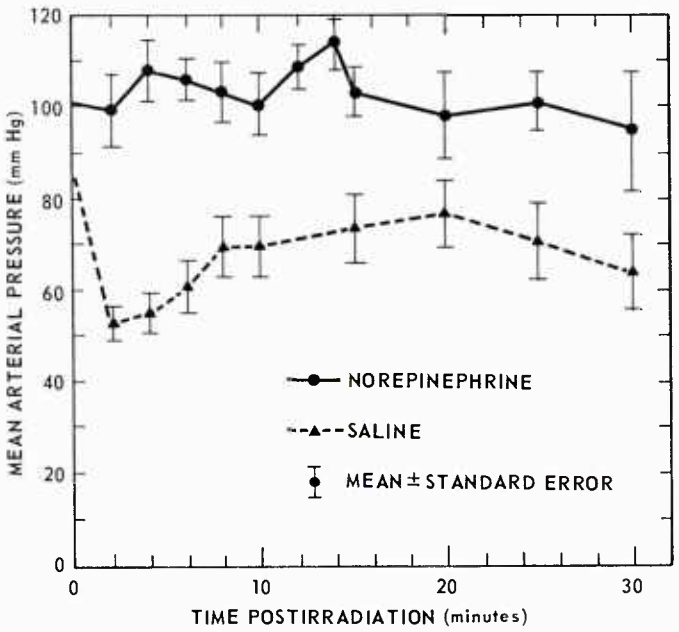


Figure 1. Average mean arterial blood pressure of monkeys infused with isotonic saline or norepinephrine following 4000 rads of mixed gamma-neutron radiation. Each group was composed of 10 animals.

performance decrement of at least moderate severity (less than 75 percent correct responses). Blood pressures of the norepinephrine-treated animals generally remained near preirradiation values; however, at least moderately severe performance decrement occurred in six of these ten animals within 4 minutes postirradiation

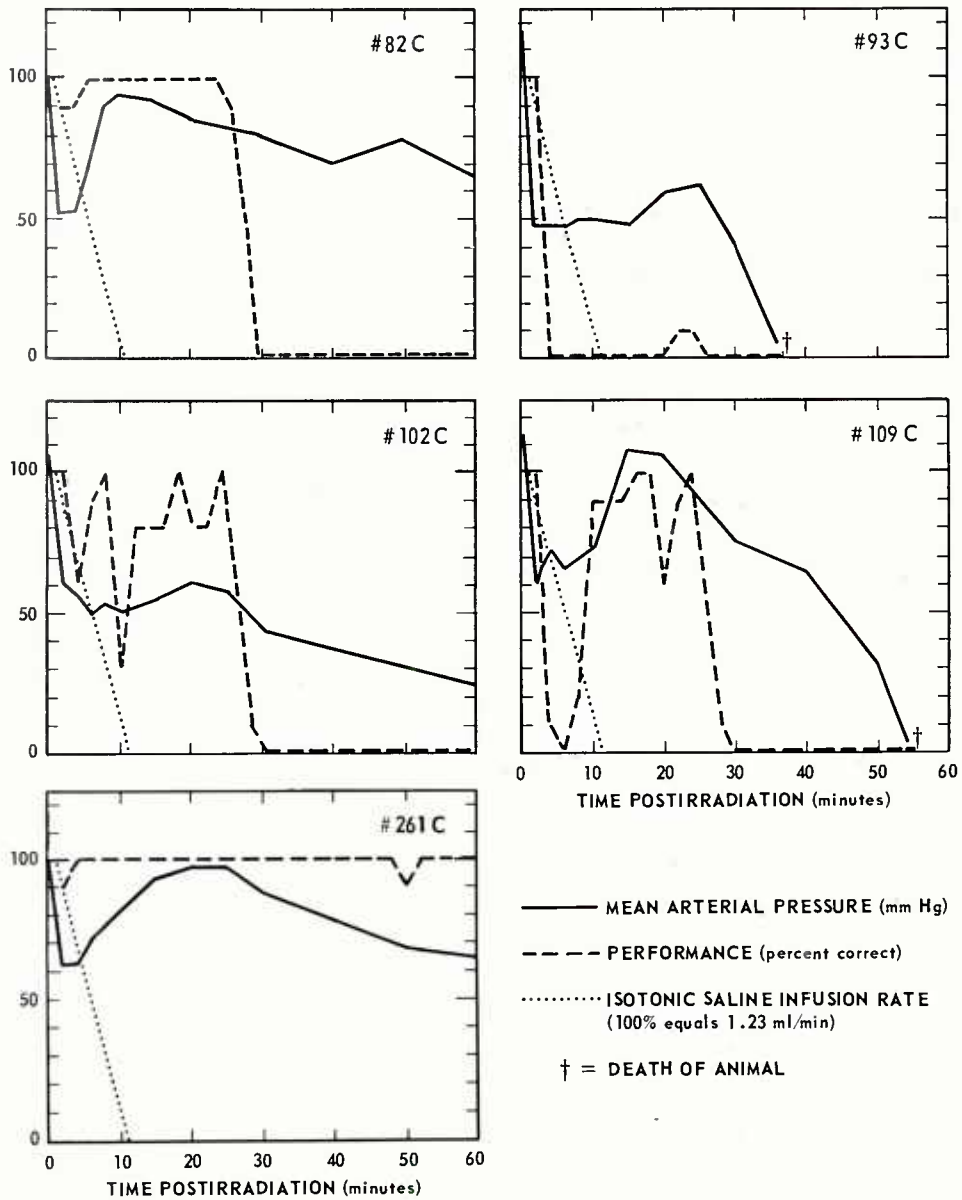
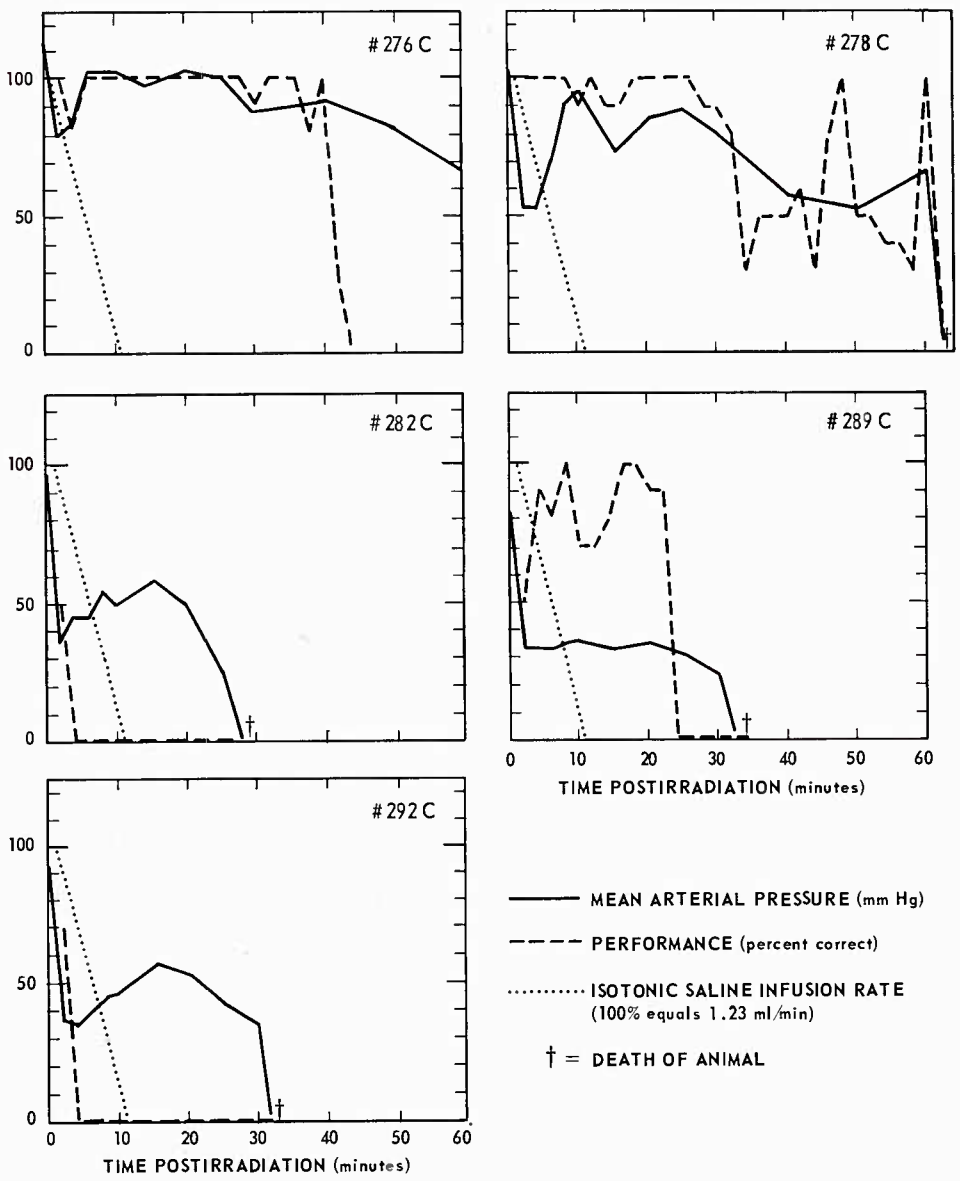


Figure 2. Mean arterial pressure, performance, and isotonic saline infusion rate of monkeys irradiated with 4000 rads of mixed gamma-neutron radiation

(Figures 1 and 3). The difference between the average performance of the two groups of monkeys was not significant at any time during the first 30 minutes postirradiation (Figure 4).



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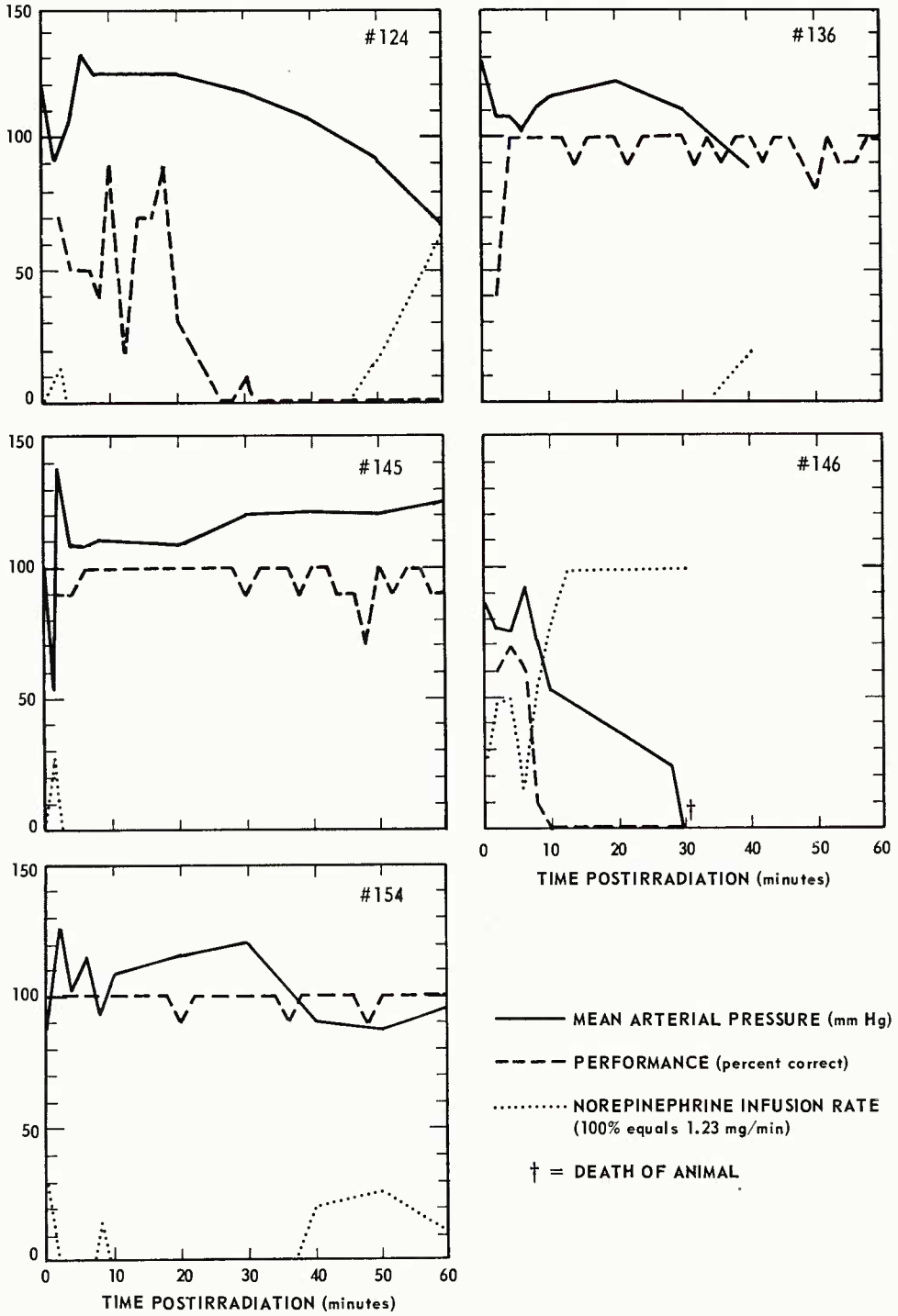
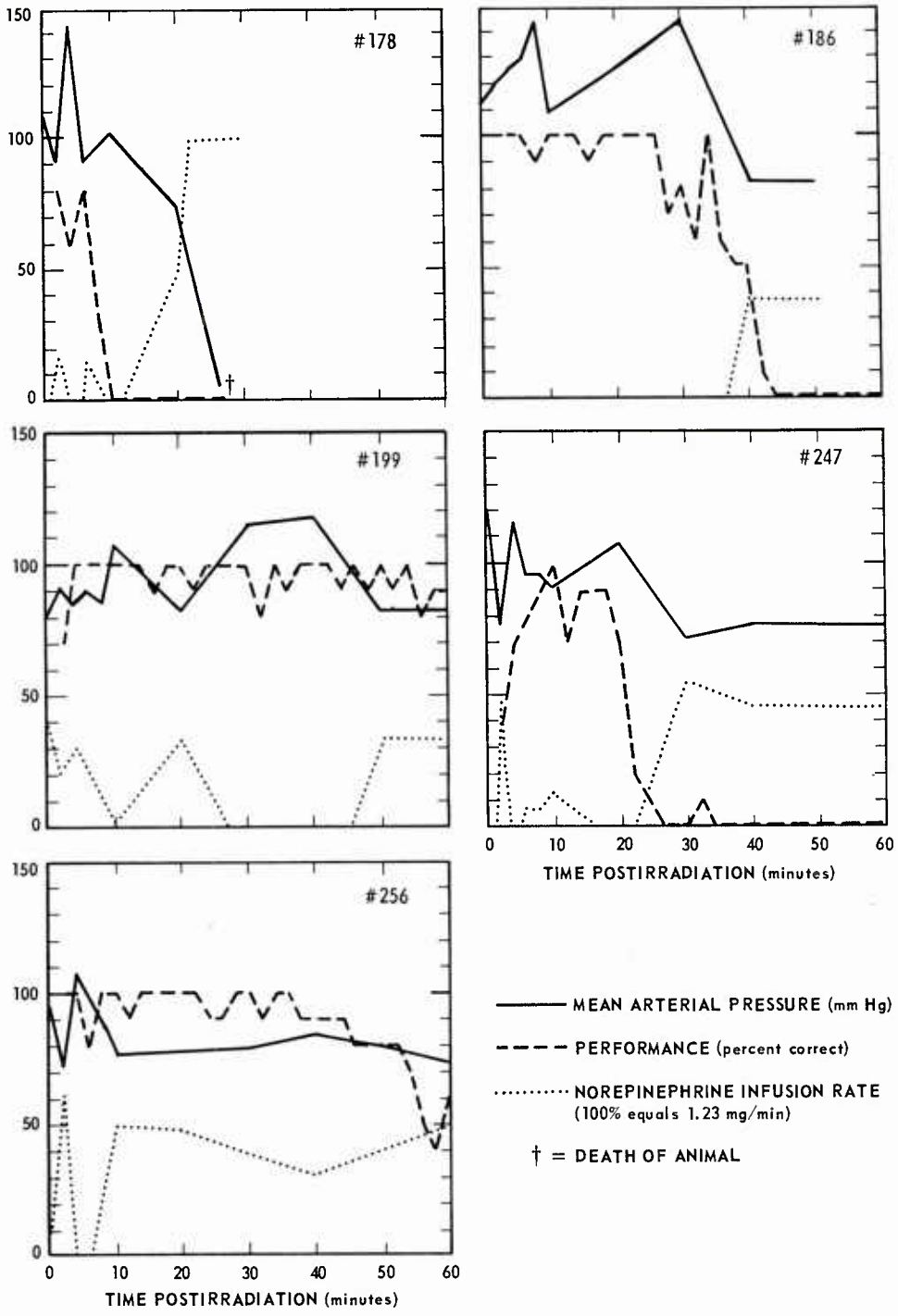


Figure 3. Mean arterial pressure, performance, and norepinephrine infusion rate of monkeys irradiated with 4000 rads of mixed gamma-neutron radiation



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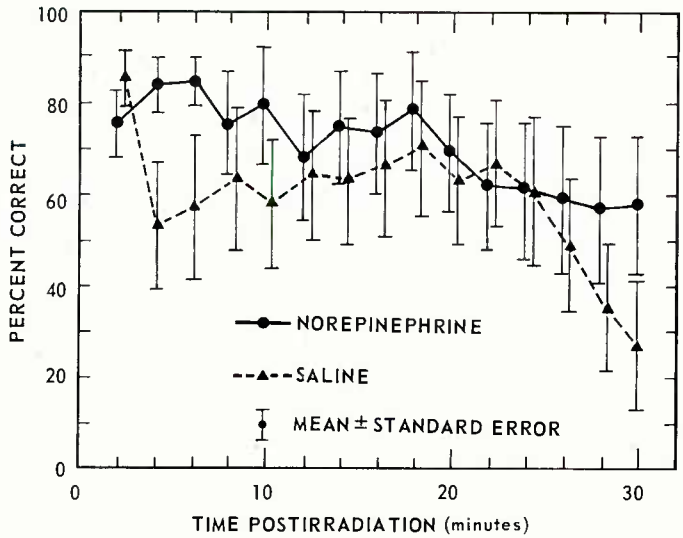

Figure 4. Average performance of monkeys infused with isotonic saline or norepinephrine following 4000 rads of mixed gamma-neutron radiation. Each group was composed of 10 animals.

Severe performance decrement, less than 50 percent correct responses, occurred in six of the treated animals (124, 136, 146, 178, 186, and 247) during periods when blood pressure was considered to be within acceptable limits, i.e., above 60 percent of preirradiation values (Figure 3).

One of the control animals, 289C, continued to perform at or above 70 percent correct from 4 to 22 minutes postirradiation while its mean arterial pressure was only about 40 percent of preirradiation values.

The mean survival time of the norepinephrine-treated animals (9 ± 4.5 hours) did not differ significantly from that of the control animals (20 ± 13 hours).

IV. DISCUSSION

Important factors in the maintenance of consciousness are adequate cerebral blood flow and cerebral oxygen consumption.[2] In man, cerebral circulation is relatively unaffected by blood pressure until the blood pressure falls below a critical level

of approximately 50 to 60 percent of normal mean arterial pressure. Blood pressures below this level diminish cerebral blood flow enough to cause clinical signs of cerebral hypoxia; loss of consciousness, or incapacitation, correlates roughly with decreased oxygen consumption.[4]

In normotensive individuals, norepinephrine moderately reduces cerebral blood flow by increasing cerebral resistance;[2] however, during hypotension, norepinephrine increases blood pressure proportionately more than cerebral resistance is increased resulting in a net increase of cerebral blood flow.[6]

The adverse effects of norepinephrine must also be considered. In the presence of exogenous norepinephrine, cardiac and cerebral blood flows are maintained at the expense of splanchnic and skeletal circulation and, if this state is sufficiently prolonged, ischemia, anoxia, tissue necrosis and lethal shock develop.[3] In the present study, the deleterious effect of norepinephrine appeared evident in that the survival time of the treated subjects was reduced when compared to that of the control animals.

Norepinephrine was generally effective in maintaining the blood pressure of the monkey for some time after irradiation; however, the difference in postirradiation performance between the norepinephrine- and saline-treated animals was not statistically significant at any time.

V. CONCLUSION

Norepinephrine, while effective in maintaining postirradiation blood pressure, is ineffective in preventing a performance decrement following irradiation. Severe hypotension may be a limiting factor to the maintenance of adequate performance postirradiation; however, radiation-induced performance decrement can occur even when blood pressure levels are well above what have been considered critical levels.

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c. Task and Subtask C 906	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d. Work Unit 01	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Director Defense Nuclear Agency Washington, D. C. 20305

13. ABSTRACT

Monkeys, trained to perform a discrete trial, cued avoidance task, were used to measure the effectiveness of intravenously infused norepinephrine in preventing the hypotension and performance decrement which usually follows 3000- to 30,000-rad doses of radiation. After a 4000-rad dose of mixed gamma-neutron radiation, 10 animals were infused with norepinephrine at a rate designed to maintain mean arterial blood pressure at approximately 100 mm Hg; for comparison 10 control animals were infused with only isotonic saline after similar irradiation. Norepinephrine, although generally adequate for maintaining blood pressure, did not consistently improve performance during the first 30 minutes postirradiation.

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