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Department of the Army
Contract No. DA-49-007-MC-428

A STUDY OF THE EFFECTS OF TOTAL AND PARTIAL BODY RADIATION ON IRON METABOLISM AND HEMATOPOIESIS

PROGRESS REPORT FOR PERIOD
1 September 1958 - 30 November 1958

Investigators: V. P. Collins, M.D.
C. T. Teng, M.D.
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ABSTRACT

1. Preparing Institution: Baylor University College of Medicine and Jefferson Davis Hospital, Houston, Texas

2. Title of Report: A Study of the Effects of Total and Partial Body Radiation on Iron Metabolism and Hematopoiesis

3. Principal Investigators: Vincent P. Collins, M.D., C. T. Teng, M.D. Walton D. West, M. Sc.

4. 14 pages, 5 illustrations, November 30, 1958

5. Contract Number: DA-49-007-MD-428

6. Supported by: Research and Development Division
Office of the Surgeon General
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Washington 25, D.C.

7. ~~Previous~~ experiments dealing with the effect of irradiation of blood in extracorporeal circulation, and with the effect of transfusion in normal dogs ~~with~~ plasma from animals previously subjected to irradiation of blood in extracorporeal circulation, ~~have been~~ were reported. In some animals, there was increased erythropoiesis over a prolonged period. ~~These observations warranted further study and the present report gives the details of an intensive investigation of this subject.~~ The method of achieving extracorporeal circulation by means of a heart-lung pump is described, and the dose of irradiation was calculated to be 10,850 gm.-r/cc of circulating blood. Observations on hematopoiesis were carried out daily for one week prior to the experiment, and the experimental animals were followed for a minimum period of three months. Results are evaluated on the basis of traumatic stimuli.

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PROGRESS

The first experiments in irradiation of blood in extracorporeal circulation were carried out in this department in November 1956 when the heart-lung apparatus became available. After technical problems were solved, the experiments were continued for the purpose of determining the effect on hematopoiesis of radiation exposure on a single tissue (blood). (This is the converse circumstance to one that has been extensively investigated, i.e., where the attempt has been to protect one tissue (bone marrow or spleen) while exposing the rest of the body to radiation). After massive exposures to amounts of radiation ranging from 3000r to 12,000r to blood circulating extracorporeally through a heart-lung pump, blood studies show an increase in erythropoiesis over a prolonged period. Normal animals receiving transfusion of plasma from dogs previously subjected to extracorporeal blood irradiation showed a similar response.

At Marquette University a similar study was carried out on both dogs and rabbits. Circulating blood was exteriorized through a polythylene tube and the tube was exposed to the x-ray beam; the dosage of irradiation is not known it is not likely that it exceeded 12,000r. The authors report, ".... white counts were chronically high during the three months following the irradiation and at the end of three months, red cell counts and hematocrits were above normal". (J. P. O'Brien, E. J. Frank, H. B. Benjamin and G. E. Bartenbach. Irradiation of solely the circulating blood of mammals. Anatomical Record 128; 597, July 1957).

These observations warranted further study to confirm or deny that irradiation of circulating blood alone is followed by a stimulation of formation of red blood cells and hemoglobin.

NATURE OF THE EXPERIMENT

Observations are being made on the hematopoietic response under two circumstances.

1. The effect of irradiation of blood in extracorporeal circulation. As a control study, similar observations are made following extracorporeal circulation of blood without irradiation.

2. The effect on normal dogs, of transfusions with plasma from dogs previously subjected to irradiation of blood in extracorporeal circulation. As a control study, similar observations are made following transfusion with plasma from normal dogs and from dogs subjected to extracorporeal circulation of blood without irradiation.

MATERIAL STUDIED

Group 1. Four animals were subjected to irradiation of blood in extracorporeal circulation and were followed for 3 months.

Group II. Four dogs were subjected to extracorporeal circulation without irradiation of blood (controls for group 1).

Group III. Six normal dogs were transfused with plasma from dogs that had previously been subjected to irradiation of blood in extracorporeal circulation (six dogs subjected to irradiation of blood in extracorporeal circulation were sacrificed to provide this plasma).

Group IV. Four normal dogs were transfused with plasma from normal dogs (four normal dogs were sacrificed to provide this plasma).

Technique of extracorporeal circulation of blood.

The dogs were anesthesized with nembutal and heparinized to prevent clotting. A cut-down was performed to the jugular vein and a No. 14 French

oxygen cathether was inserted in the vein; a second cut-down was done to the carotid artery with insertion of a No. 12 catheter. The extra-corporeal pump was connected to the arterial catheter with tygon tubing. From the pump blood was circulated to a 500cc. plastic reservoir bottle and returned to the animal by was of the venous catheter through tygon tubing. The system was primed with 500cc. of normal saline and the pump was adjusted to a flow of 300-350 cc. per minute.

Technique for irradiation of blood in extracorporeal circulation.

With the animal under anesthesia and the heart-lung apparatus working satisfactorily, the dog was placed approximately 5 feet from the 2 MeV. Van de Graaff generator with the beam directed vertically downward. The length of tygon tubing was sufficient to allow the reservoir to be placed within the head of the x-ray generator with the animal well away from the beam. The shutter was closed against the reservoir to minimize the emerging radiation. The area was checked with an ionization chamber and scatter radiation was found to be 1.1r/40 minutes (4500 metered out put) 5 feet from the machine thus assuring adequate protection of the dog's body against significant amounts of radiation.

After circulation and irradiation, the reservoir is removed from the head of the Van de Graaff generator and placed on a clamp stand. The catheter is removed from the carotid artery and the blood remaining in the reservoir and tubing is pumped back into the dog through the venous cut-down. The venous catheter is removed and the jugular vein is tied off.

Calculation of Radiation Dosage

When the reservoir bottle is placed within the head of the Van de Graaff the distance from the target to the surface of the blood is 24.5 cm. The intensity of the beam being 1600r/minute then the average exposure in roentgens per volume of blood (D_{avg}) is:

$$D_{avg} = \frac{V_b \times r_m \times F \times P}{V_B}$$

where: V_b = volume of blood in the reservoir

V_b = total volume of blood being circulated

r_m = metered output in roentgens at 81.7 cm.

F = inverse square correction factor for exposure in roentgens at surface of blood being irradiated.

P = average depth dose in percent of surface dose.

For example, let metered output (r_m) equal 1 roentgen, V_b equal 396 cc. (constand for all dogs), F equal 12.5 (constant for all dogs) and P equal to 0.77 (constant for all dogs). V_b is variable for each dog but would average approximately 1400 cc. Substituting these values into the formula we get:

$$D_{avg} = \frac{396 \times 1 \times 12.5 \times 0.77}{1400 \text{ cc.}} = 2.722 \text{ gm- r/cc.}$$

In the experiment, each dog received 50,000r total surface dose where the total surface dose is equal to $r_m \times F$. Inserting this into the average dose equation:

$$D_{avg} = \frac{396 \times 50{,}000 \times .77}{14{,}000} = 10{,}850 \text{ gm-r/cc.}$$

Technique for collection and transfusion of plasma.

Two pints of blood are collected by way of a heart puncture into exacuated 650cc. transfusion bottles with 12% ACD anti-coagulent. The blood is stored in the refrigerator over night before being contrifuged. The plasma is aspirated from above the packed red cells into a 250 cc. evacuated plasma collection bottle.

The plasma is administered intra-venously at the rate of approximately 5 cc. per minute. Sterile technique is observed though out the entire procedure of collection and transfusion.

Hematologic observations.

Both groups of dogs, experimental and control, were observed by hematological determinations daily for a minimun period of one week prior to use in the experiment. Following their use in the experiment, counts were performed immediately and two hours afterwards. Daily counts were then performed for one week. After the first week, the time was extended to twice weekly through four weeks post experimental day and then extended to every other week for two additional months. Other than the counts reported in graphical form, hematocrits and differentials were performed on the above schedule. The average daily determinations taken prior to the use in the experiment was used as the base line of 100%.

Results

Fig. 1 A The response of red blood cell count in 4 animals subjected to irradiation of blood in extracorporeal circulation. (Group 1). Following an initial prompt depression, there are erratic variations in red blood cell count for three weeks before recovery is clearly evident. During the next six weeks, the red blood cell count increases, and at 2 months following the initial procedure all four animals have returned to normal while two are more than 25 per cent above the initial level.

Fig. I B The response of red blood cell count in 4 dogs subjected to extracorporeal circulation without irradiation. (Group II). There is an immediate and uniform fall in red blood count with recovery to normal levels in all cases within a week. Thereafter, one animal showed a persistent elevation of 15-30 per cent in red blood cell count and one had a sudden elevation of 30 per cent more than two months following the procedure of extracorporeal circulation of blood.

Fig. 2 A The response of hemoglobin levels in 4 dogs subjected to irradiation of blood in extracorporeal circulation. (Group I). There is a prompt fall in hemoglobin reaching its lowest point at 2 - 3 weeks. Thereafter, all dogs show a steady rise to normal and in 2 of 4 dogs, this continued to reach levels of 30 to 50 per cent above initial values after 2 months.

Fig. 2 B The response of hemoglobin in 4 control animals subjected to extracorporeal circulation of blood without irradiation.(Group II). There is an immediate and uniform depression of hemoglobin but recovery begins within hours and reaches normal in 3 weeks. Thereafter, values continue at approximately normal levels although some elevation occurs after 2 months.

Comments

The total procedure of extracorporeal circulation with or without irradiation of blood in extracorporeal circulation is apparently a form of trauma inducing an immediate depression of red blood cell count and hemoglobin. The depression following extracorporeal circulation alone is at least as immediate and profound as in the cases that also received irradiation. However, the recovery to normal levels following extracorporeal circulation alone is prompt and there is some suggestion that

values for red blood cell count and hemoglobin may swing above normal during the next 2 months. Following extracorporeal circulation plus irradiation, recovery to normal level required approximately 3 weeks. Thereafter, there is a stronger suggestion that recovery swings well above initial levels for both red blood cell count and hemoglobin during the next 2 months.

Fig. 3 A The effect of red blood cell count in 6 normal dogs, of transfusion with plasma from sacrificed dogs previously subjected to irradiation of blood in extracorporeal circulation of blood. (Group III). There is an initial depression with irregular recovery. One animal of six showed depression persisting for 3 months; one animal showed elevation persisting for 3 months. Five of six animals showed depression at 30 days, 5 of 6 animals showed recovery to above normal levels at 60 days.

Fig. 3 B The effect on red blood cell count in 4 normal dogs, of transfusion with plasma from sacrificed dogs previously subjected to extracorporeal circulation of blood without irradiation. (Group III). These animals show the same initial depression following transfusion and recovery is prompt. Approximately normal levels are maintained for the next two months. In comparison with the animals receiving irradiated plasma and showing some elevation of red blood cell count at 2 months, the animals receiving non-irradiated plasma all show a red blood cell count very slightly below the initial levels after 2 months.

Fig. 4 A The effect on hemoglobin, in 6 normal dogs, of transfusion with 500 cc. plasma from sacrificed dogs previously subjected to irradiation of blood in extracorporeal circulation. (Group III). There is prompt depression of hemoglobin levels with slow recovery. At 3 weeks all animals show hemoglobin below the initial level; at 6 weeks, 3 are above and 3 are below the initial levels. At 2 months five or six are above initial levels.

Fig. 4 B The effect on hemoglobin, in 4 normal dogs, of transfusion with 500 cc. plasma from sacrificed dogs previously subjected to extracorporeal circulation of blood without irradiation. (Group III). There is an immediate fall in hemoglobin with beginning recovery evident at 2 hours. Recovery to normal levels occurred in 4 dogs and thereafter hemoglobin levels are maintained at the initial levels during the next two months.

Comments

Transfusion with plasma from dogs previously subjected to extracorporeal circulation with or without irradiation is followed by an immediate drop in hemoglobin. Recovery to initial levels is prompt and maintainta when the transfusion is with plasma from dogs subjected to extracorporeal circulation without irradiation. When transfusion is with plasma from dogs subjected to irradiation of blood in extracorporeal circulation, recovery to initial hemoglobin levels is delayed for about 3 weeks and thereafter a rise above normal levels gradually occurs and is still present after 2 months.

Fig. 5 A The effect on red blood cell count, in 4 normal dogs, of transfusion with 500 cc. plasma from sacrificed normal dogs. (Group IV). There is an immediate depression of red blood cell count with recovery to initial levels after one day. Thereafter, irregular fluctuations occur so that at one month two animals show red blood cell counts 10 - 15 per cent above initial levels and two are 15 - 25 per cent below. At two months all four animals show red blood cell counts at or slightly above the initial levels.

Fig. 5 B The effect on hemoglobin, in 4 normal dogs, or transfusion with 500 cc. plasma from sacrificed normal dogs. (Group IV). There is immediate depression of hemoglobin levels with recovery to initial levels in 1 - 2 days. Thereafter values are closely related to initial levels although at 30 days one animal had a hemoglobin level 16 per cent above initial level and one

was 22 per cent below initial level. At 2 months all values are at or slightly above the initial values.

Comments

Transfusion with serum of normal dogs induces an immediate drop in red blood cell count and hemoglobin with prompt recovery to normal levels. At 60 days after transfusion, all animals are at, or very slightly above, the initial level for red blood cell count and hemoglobin.

DISCUSSION

The initial purpose of this experiment was to determine whether irradiation of one tissue)blood) alsone would produce any effect than might clarify the nature of radiation injury in higher animals. Irradiation of the entire animal or even of localized areas includes many different tissues. A radiation effect on one tissue may be masked by radiation effects on other tissues. A radiation effect one one tissue may be masked by interaction between normal and injured tissues. An effect observed followigg radiation may be a non-specific systemic response secondary to radiation injury sustained by the irradiated tissue.

Initial observations indicated that the mere subjection of the animal to extracorporeal circulation of blood as used for the purposes of cardiac surgery products no deleterious reaction.

When the blood in extracorporeal circulation was subjected to intensive radiation, no immediate deleterious effect was observed but when these animals were observed for periods of 2 to 3 months, an unexpected rise in hemoglobin and red blood cell count occurred. This seemed an unlikely effect of radiation exposure of any kind but because of its possible significance for clarifying the nature of tissue response, it was necessary to repeat the experiment with more satisfactory controls.

The present studies show immediate fall in hemoglobin and red blood cell counts following transfusion with plasma from normal dogs, following transfusion of plasma from dogs subfected to extracorporeal circulation of blood with and without radiation, and in dogs subjected to extracorporeal circulation with or without irradiation. A change of this nature is an understandable dilution effect from the addition of 500 cc. of plasma in the transfusion experiments and of 500 cc. of saline that the animal received in the course of priming the pumping system for extracorporeal circulation. This can be looked upon as a form of trauma. The present experiment was not designed to test the magnitude of trauma in relationship to the type and severity of response.

Some variagion in the immediate recovery was observed. Those transfused with 500 cc. of normal plasma show immediate recovery in the first day and no appreciable variation from initial levels when followed for periods up to 3 months.

Animals transfused with plasma obtained from sacrificed animals previously subjected to extracorporeal circulation showed an equally prompt immediate recovery. When these animals were followed for periods up to 3 months, there was no dramatic variation from initial levels.

When normal dogs are transfused with plasma from sacrificed dogs that had been subjected to irradiation of blood in extracorporeal circulation the recovery is less prompt and there are erratic variations during the first month. Thereafter, there is a general recovery to values from 5 to 20 per cent above normal levels at 3 months.

In animals that have been subjected to extracorporeal circulation without irradiation, there is prompt recovery from the initial depression and there after values continue at or slightly above the initial levels.

In animals that have been subjected to irradiation of blood in extracorporeal circulation, depression and erratic variation mark the hemoglobin and red blood cell count values for the first month. Thereafter, there is a general rise so that at 3 months, all values are above normal and two of four have reached 30 per cent.

In this series of animals, there is demonstrated a clear injury and recovery phenomenon.

Transfusion with 500 cc. of plasma from normal dogs appears to represent a minimal and inconsequential injury and recovery.

Transfusion of animals with plasma from sacrificed animals subjected to extracorporeal circulation without irradiation does not differ appreciably from transfusion with plasma from normal dogs.

Transfusion with plasma obtained from dogs previously subjected to extracorporeal circulation plus irradiation produced a more prolinged depression followed by a prolinged recovery to above normal levels.

Animals subjected to extracorporeal circulation of blood without irradiation showed prompt recovery and continued to maintain levels at or slightly above initial values for hemoglobin and red blood cell counts.

Animals subjected to irradiation of blood in extracorporeal circulation show a more prolinged depression of hemoglobin and red blood cell count values with gradual recovery to above normal levels.

SUMMARY

This study demonstrates the response of red blood cell count and hemoglobin levels to three types of interference that may be looked upon as traumatic stimuli.

1. Plasma transfusion
2. Extracorporeal circulation of blood
3. Irradiation of blood in extracorporeal circulation

These represent different magnitudes of trauma; transfusion is minimal, extracorporeal circulation somewhat greater, and irradiation of blood in extracorporeal circulation seems distinctly to add an additional factor to injury.

Injury is followed by recovery. For a more severe injury, recovery tends to achieve levels above initial values for hemoglobin and red blood cell counts.

Whether the addition of irradiation in these experiments represents merely quantitatively greater trauma, or whether it is qualititively different trauma, is not established. The observation of similar prolongation of depression and recovery in dogs transfused with irradiated plasma does permit the possibility that blood irradiated in extracorporeal circulation does sustain injury beyond that due to the mechanical procedure alone.

FUTURE

As commonly happens in following one course of investigation, secondary investigations are suggested. We are left with several questions to consider.

1. Do the components of whole blood sustain a specific type of damage when subjected to intensive radiation?
2. If so, can this injury be identified by an alteration in blood itself or by its effect upon other body tissues or systems?
3. Can the phenomenon of injury and repair as demonstrated by the hematopoietic system be used to distinguish qualitative and quantitative differences in injury involving radiation?
4. Is there an element of injury to hematopoiesis inherent in the use of transfusion and the use of intravenous fluids?

5. Would repeated episodes or chronic trauma lead to exhaustion of reparative powers and aplastic anemia?

While it is not certain that radiation is an important factor in the response observed, the physiological mechinism itself merits further study. The direction of further observations will be to attempt to exaggerate the effect by increasing the magnitude of the immediate trauma and by repeated or protracted trauma. This would be an anticipation of producing more impressive recovery to above normal levels and eventually achieving an exhaustion response following prolonged stimulation.

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Fig. 1 A. Response of Red Blood cell Count (%) in 4 Animals Following Extracorporeal Irradiation of Circulating Blood

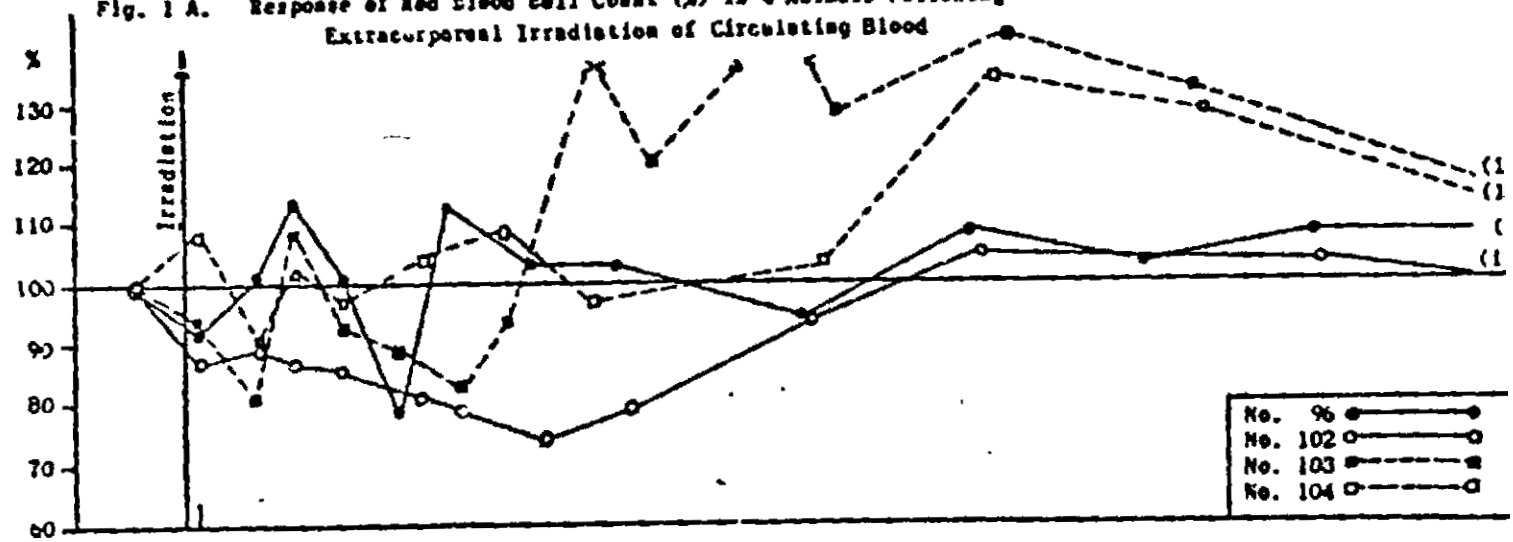


Fig. 1 B. Response of Red Blood Cell Count (%) in 4 Animals Following Extracorporeal Circulation of Blood Without Irradiation

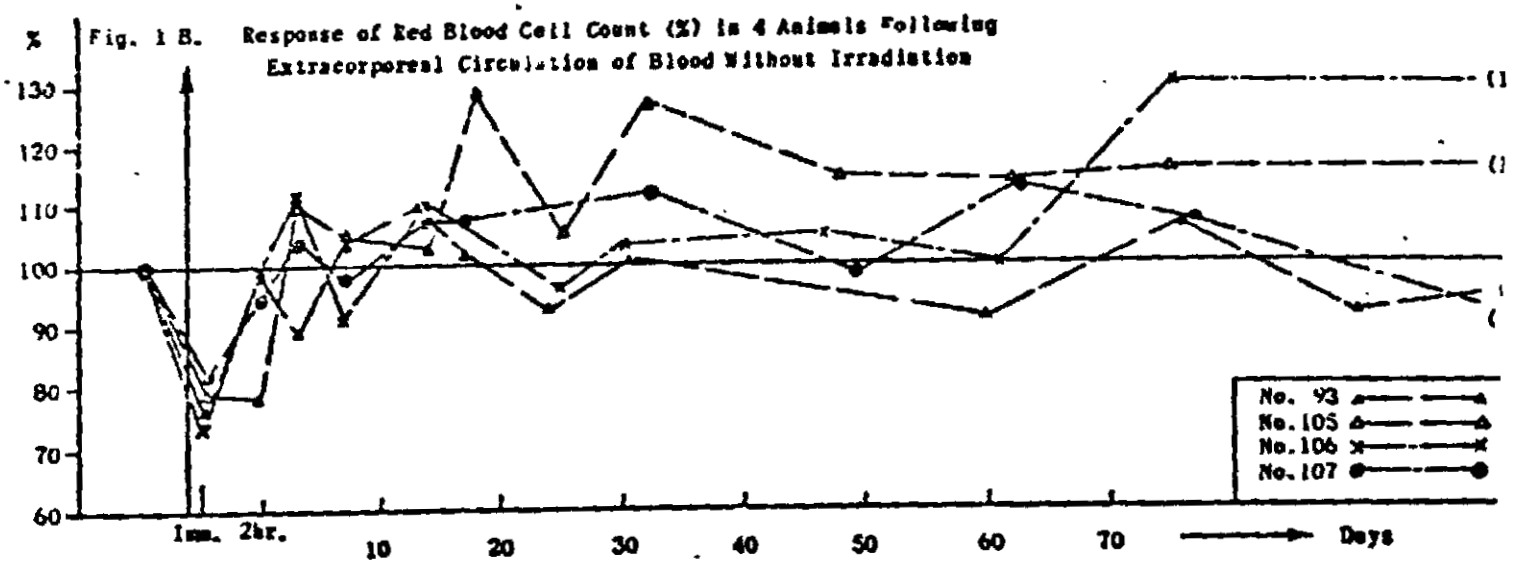


Fig. 2 A. Response of Hemoglobin (%) in 4 Animals Following Extracorporeal Irradiation of Circulating Blood

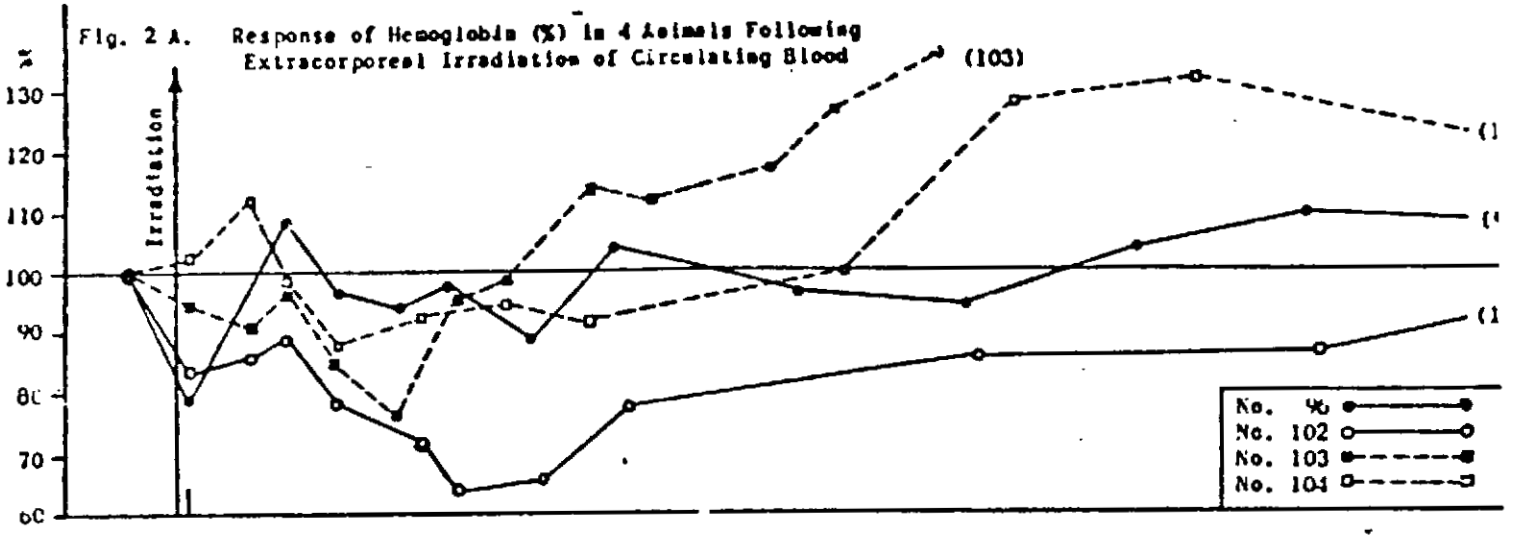


Fig. 2 B. Response of Hemoglobin (%) in 4 Animals Following Extracorporeal Circulation of Blood Without Irradiation

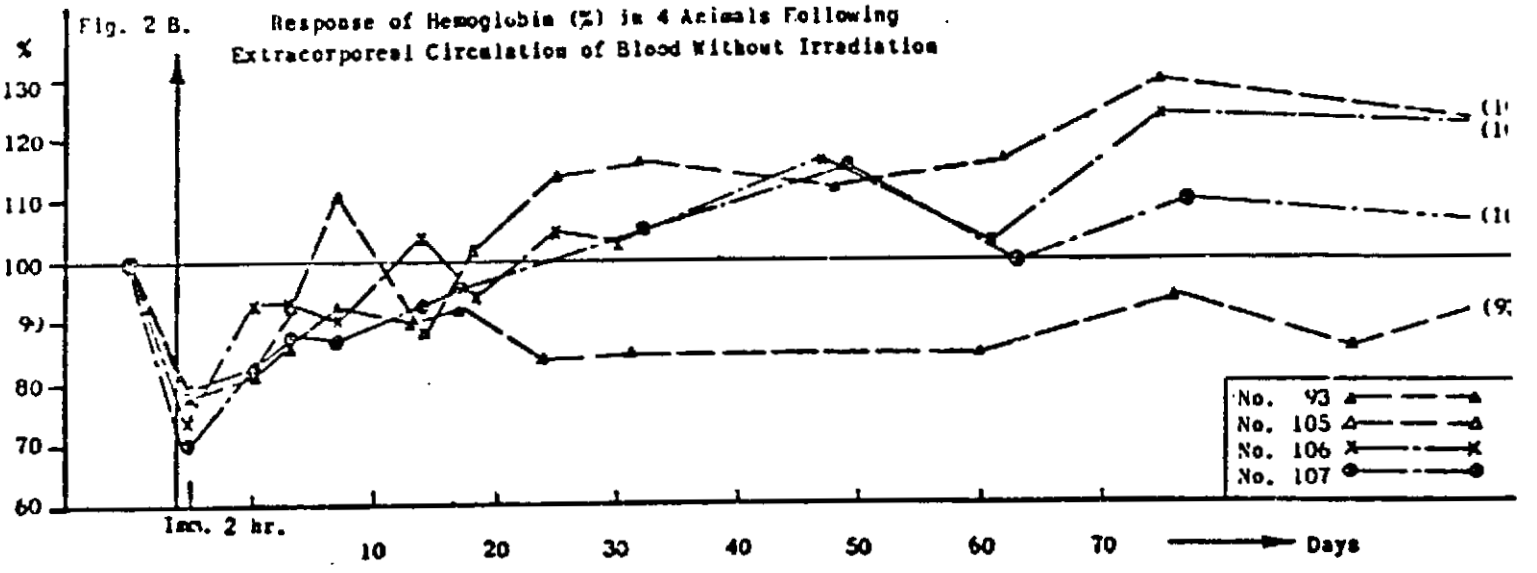
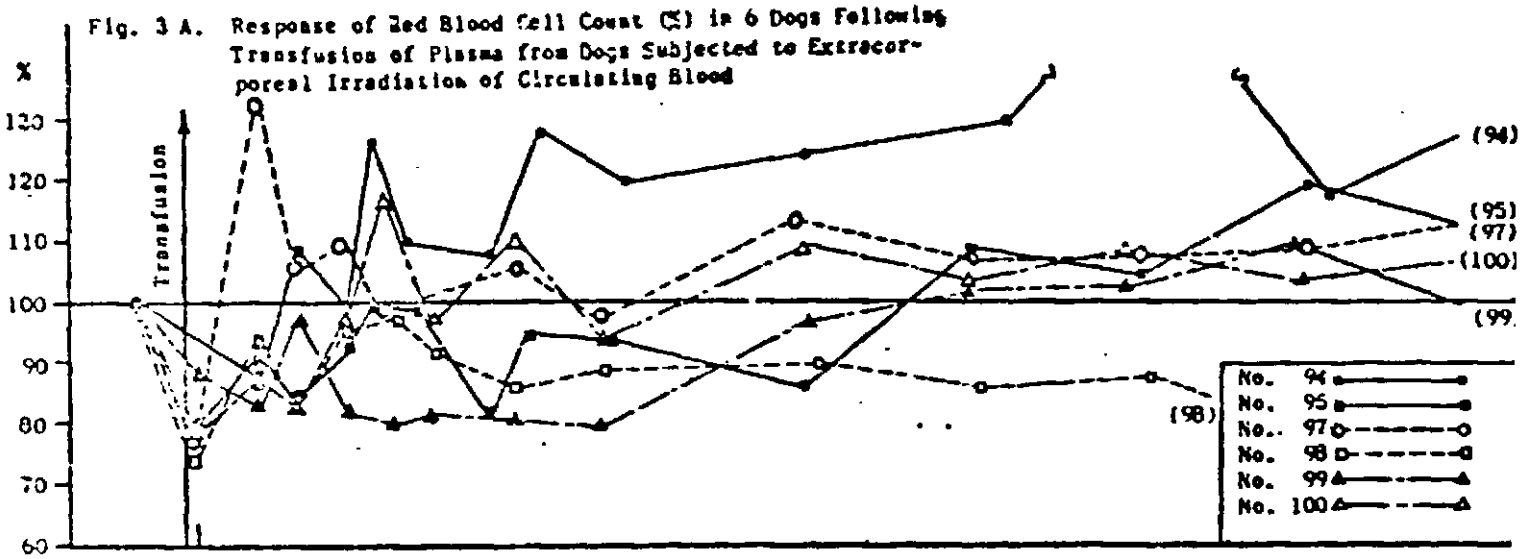


Fig. 3 A. Response of Red Blood Cell Count (%) in 6 Dogs Following Transfusion of Plasma from Dogs Subjected to Extracorporeal Irradiation of Circulating Blood



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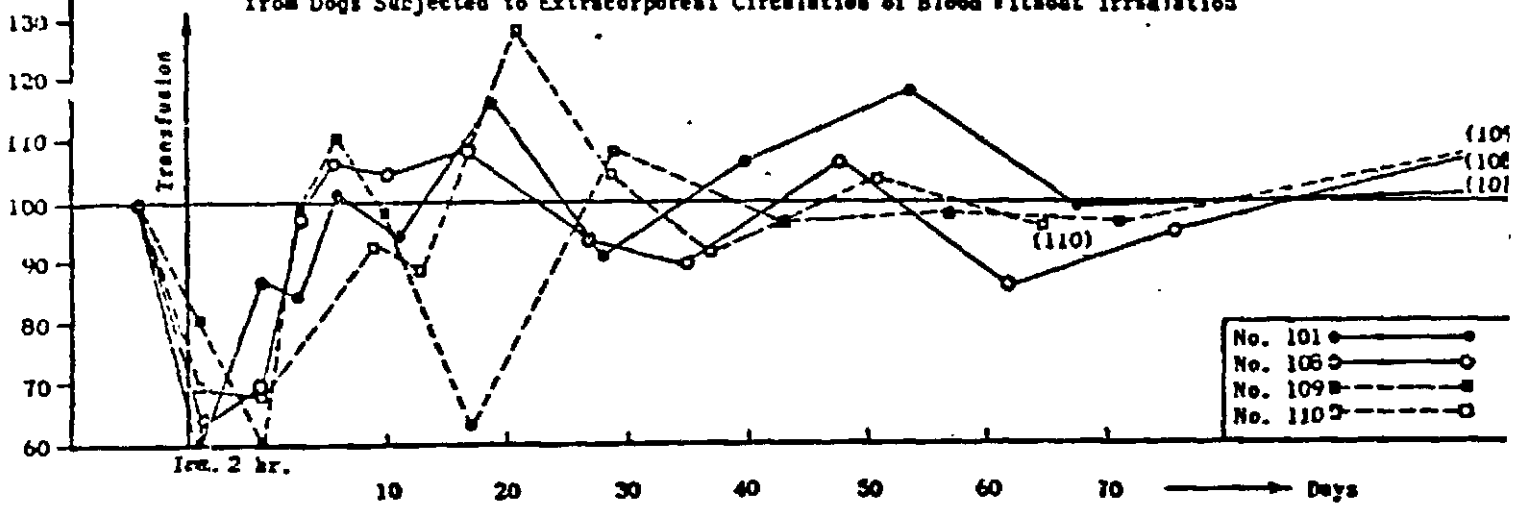

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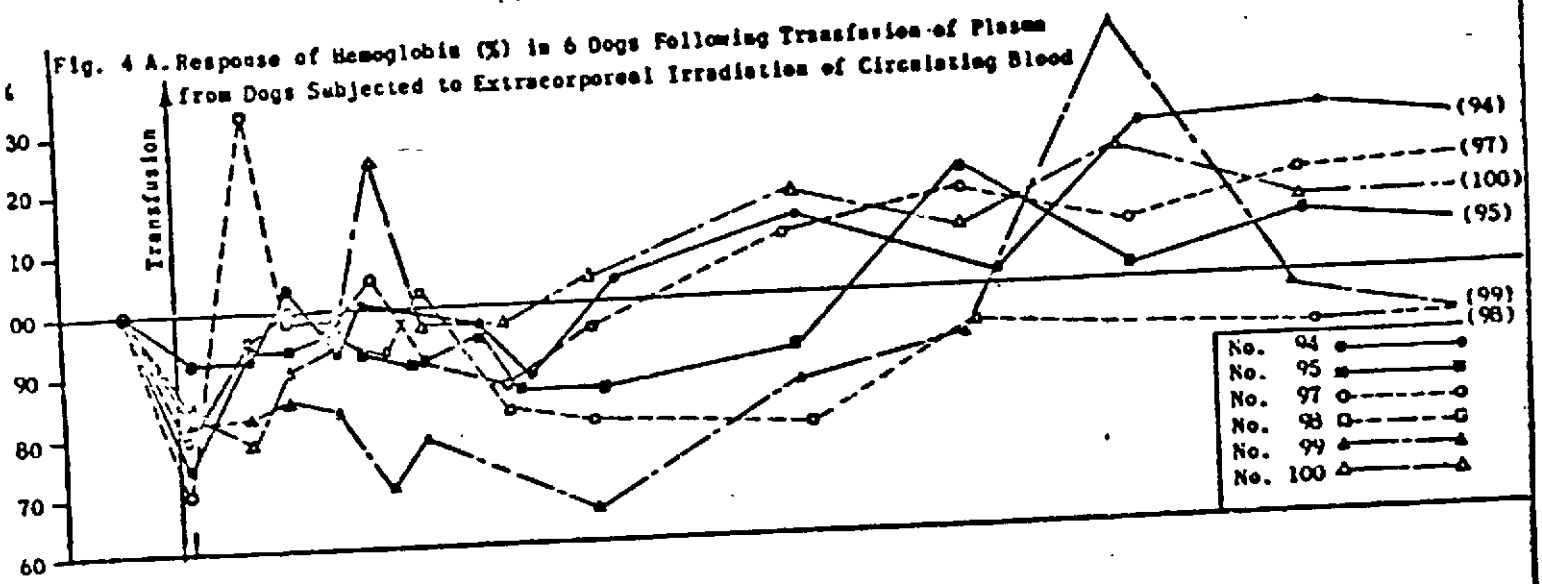


Fig. 4 B. Response of Hemoglobin (%) in 4 Dogs Following Transfusion of Plasma from Dogs Subjected to Extracorporeal Circulation of Blood Without Irradiation

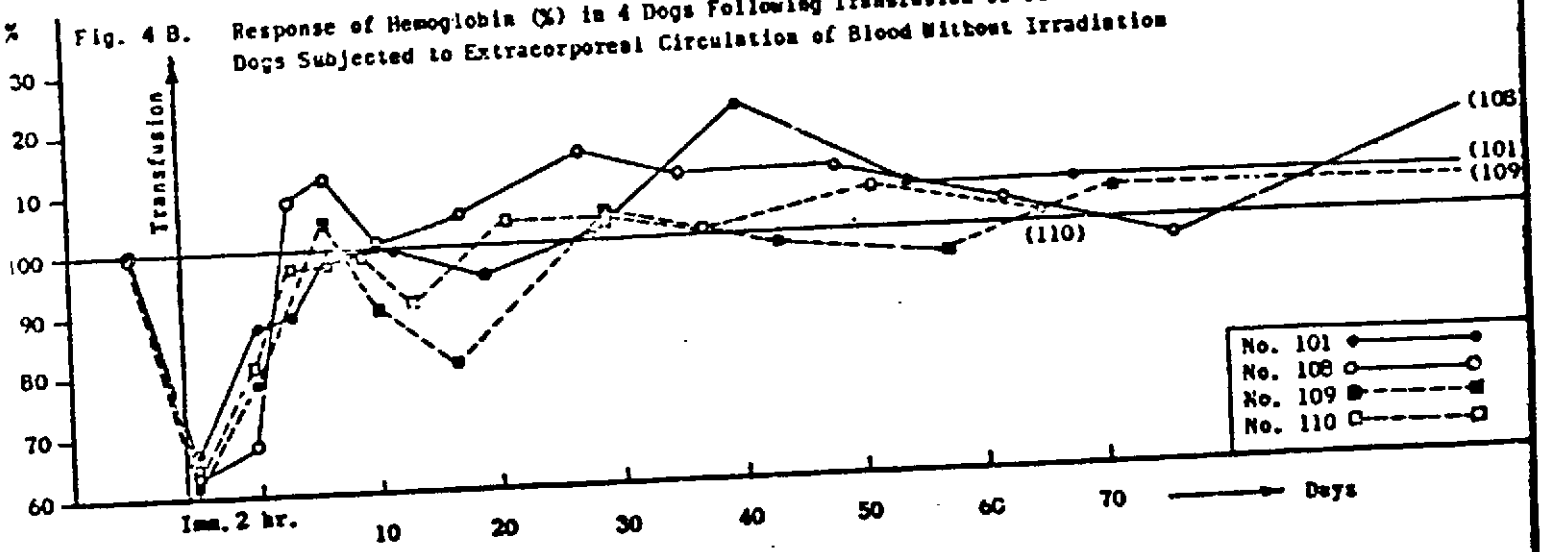


Fig. 5 A. Response of Red Blood Cell Count (%) in 4 Dogs Following Transfusion of Normal Plasma

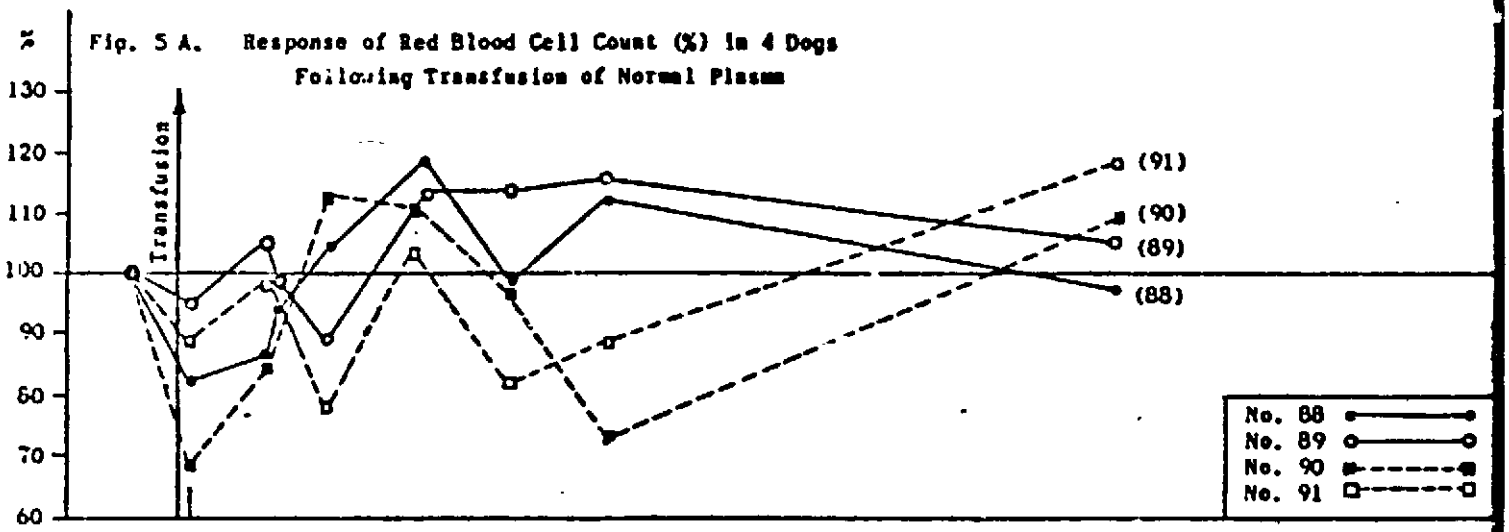
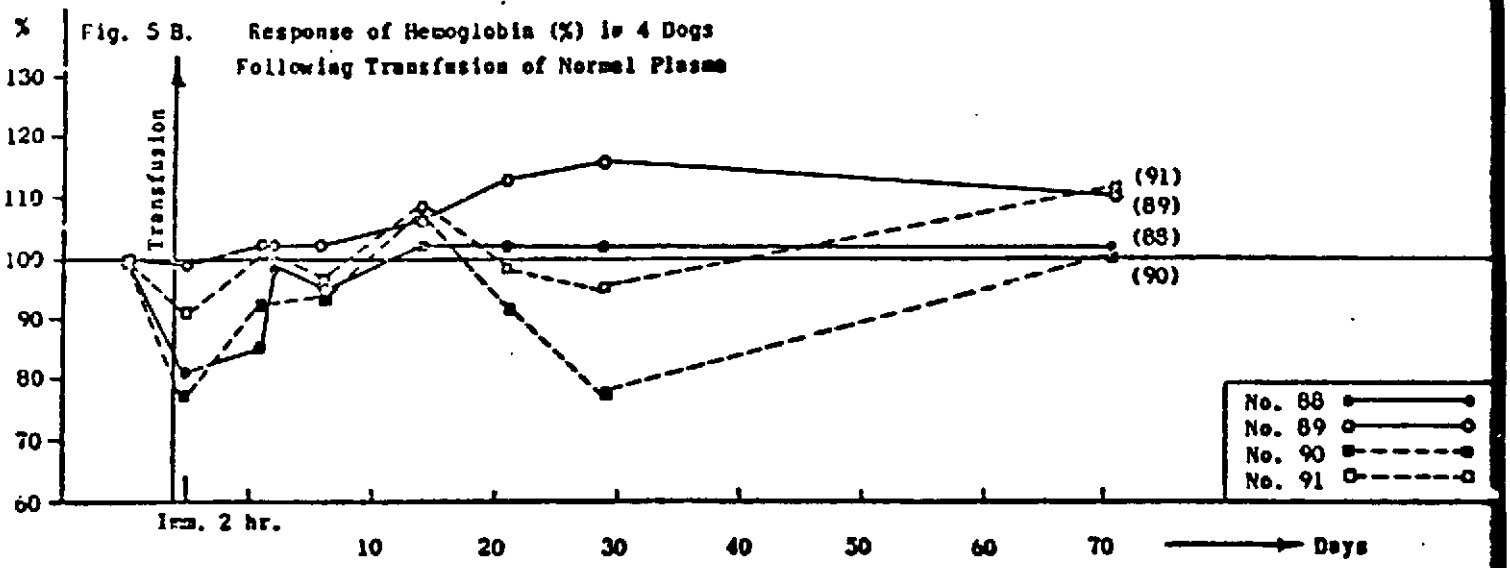


Fig. 5 B. Response of Hemoglobin (%) in 4 Dogs Following Transfusion of Normal Plasma



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