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ABSTRACT

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

4. 27 pages, 23 illustrations, March 13, 1958

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

6. Supported by: Research and Development Division
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Department of the Army
Washington 25, D. C.

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

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

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PROGRESS REPORT FOR PERIOD
1 September 1957 to 28 February 1958

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Not for publication or publication reference without approval of author and Chief, Research and Development Division, Office of The Surgeon General, Department of the Army, Washington 25, D. C.

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PROGRESS

I. Dosimetry

1.A. Calibration of the 2 MeV radiation unit (Van de Graaff generator) used in this study.

a. A monitoring ionization chamber, located in the head of the Van de Graaff generator records the output on a cumulative r-meter which is located on the control panel.

b. The cumulative r-meter is calibrated against a high energy type 621 Victoreen chamber. The output in air as measured with the Victoreen chamber at 81.7 cm. with a 10 x 10 cm. field size at this distance is arbitrarily called 100 per cent for all dose determinations.

c. The cumulating r-meter is checked against the output as measured by the ionization chamber at the treating distance of 81.7 cm., for daily control of routine partial body radiation procedures and is also checked before each total body radiation procedure.

d. The per cent of output in air at the axis of rotation is checked before each total body procedure using the rotating chair.

1.B. Calibration of the 220 KV radiation unit (Westinghouse C. P.) used in previous studies is as follows:

a. A model 70-5 Victoreen medium energy chamber is used. The output measured in air at a distance of 50 cm. and with a 10 x 10 cm. field is arbitrarily called 100 per cent (for a given filter and m.a.)

b. The output is checked daily and the time for a prescribed patient exposure for partial body radiation determined accordingly.

c. For total body radiation carried out with this unit, the exposure is measured with the Victoreen at 300 cm. at the surface of a phantom. This is exposure in air plus backscatter.

Both the H. E. and M. E. Victoreen chambers are checked against a radium source standard.

2. Partial body radiation

The calibration value for output in air as above described for the respective machines is taken to be one hundred per cent. The values for skin, tissue or tumor dose are routinely determined by use of isodose curves in which all values are expressed as a percentage of this standard calibration value.

Depth dose or absorption studies are carried out with either a presswood or water phantom using both ionization chamber and film densitometer methods.

For the ionization chamber method, we use semi-remote control equipment which permits multiple or continuous measurements to be made without turning off the x-ray unit.

For the film densitometer method, a specially designed presswood phantom permits simultaneous exposure of films placed at different depths in the phantom. Also, a specially designed densitometer permits rapid scanning of the exposed film for quanitization.

Partial body radiation dose is expressed in roentgens delivered in a stated elapsed time, a single value for the amount of radiation at the tumor site. Such a single value is meaningful only for purposes of prescription and comparison if known conventions are being followed. Our records include dimensions and dose distribution diagrams for re-evaluation at a later date, e.g., to translate roentgens to rads or to integral dose.

3. Total body radiation

The geometry is dictated by the dimensions of the treatment room and the output of the machine. The treating distance must be great enough that the entire patient is included in the diverging beam. It must be short enough

that the output and the time necessary to complete the treatment is practical and considerate of the patient.

A. With patient stationary in the beam of radiation.

When total body radiation is carried out with the 220 KV unit, the maximum target-patient distance is 300 cm. With 1 mm. Cu. and 1 mm. Al added filtration, the Hvl. in tissue is 11.6 cm. (Fig. 1). The output is 2.3 r per minute.

The patient is customarily treated while lying on his side on a stretcher facing either to or away from the x-ray machine. If only a single dose of radiation is planned, half the exposure will be made to the anterior aspect of the body and half to the posterior aspect. If multiple small doses of radiation protracted over a period of time are planned, then the patient may be treated anteriorly and posteriorly on successive treatment visits.

For 2 million volt radiation, ill or weak patients may be treated in a stationary position, lying on a stretcher as above described. Treatment will be carried out at 400 cm. distance where the cross section of the beam has a maximum dimension of 120 cm. The output at this treatment distance is 4.5 r measured in air.

For both 220 KV radiation and 2 MeV radiation, when the patient is treated in the stationary position, the dose is recorded as the dose at the surface of the patient plus backscatter. Dose is recorded in this manner because initial measurements are made in this fashion with a phantom and dose can be checked during treatment with an ionization chamber in place on the patient's skin.

B. Total body radiation with the patient rotating in the beam of radiation.

This procedure is carried out only with the 2 MeV x-ray generator. The patient is seated on a light rotating chair with the axis of rotation 4 meters from the tube target of the x-ray machine. The rate of rotation is one revolution per minute.

For this procedure, dose is recorded in roentgens, measured in air, at the axis of rotation. The chief justification for this is that the measurement can be duplicated and the exposure can be similar for different patients. The data is available for a more meaningful expression of dose to patient when agreement is reached on this aspect.

4. Integral dose

A number of published and unpublished methods have been evolved for estimating integral dose in radiation therapy. The data are usually presented in graph form as a plot of gram-roentgens / roentgens measured in air / square centimeter of body presenting, against the thickness of the part of body being irradiated. Such graphs are prepared for a given quality of radiation and are valid under restricted conditions. The approximations involved are plausible for large fields and large target-to-patient distance as obtain with total body patients. Such a curve for 2 MeV quality x-rays is included (Fig. 2).

Direct calculation of integral dose for total body radiation would require an impractical number of measurements and assumptions. The solution we have derived is based on the approximation that body weight averages one gram per cubic centimeter. Particularly for rotation therapy, thickness of patient can be expressed as an average value.

Then, - $h \times t \times t = V$ or $t = \sqrt{V/h}$

Where, - t = thickness

h = height

V = volume or weight in grams

ht = area of body surface presenting toward the x-ray source. This is the area in square centimeters. This number multiplied by N (gram-roentgens / roentgen of exposure in air) is the ordinate in the graph in Fig. 3.

The integral dose $I_d = h \times t \times N \times E$ gram-roentgen / roentgen air dose at axis of rotation for the 2 MeV unit.

Here E is a factor which corrects for the fall-off of beam intensity toward the edges and compensates for loss of energy scattered from the patient.

The total integral dose (I_t)

$I_t = h \times t \times N \times E \times R$ gm. r.

R = the number of roentgens given to air or surface as dictated by the conditions for which the graph was computed.

The procedures for integral dose then, are

1) The gm. r / r / cm^2 v.s. t graph is constructed by use of the expression -

$$I = 1.44\ D \times A \times d\tfrac{1}{2}\ (1 + R \times d\tfrac{1}{2}/F + 000)$$

Where, - D = 1 roentgen

A = 1 cm^2

$d\tfrac{1}{2}$ is found experimentally

R and F are known

I is summed up from 0 thickness to t.

2) $I_t = h \times t \times N \times E \times R$ gm. r.

3) $I_t = h \times t \times N \times E \times R \times Q$ rads - Q varies with quality of radiation beam.

In six subjects in whom the invivo and the in vitro tagging techniques have been carried out on the same day, we have demonstrated to our own satisfaction that the plasma iron disappearance curves are identical in slope and the dilution volumes agree within ∓ 5%. These results are summarized in Table 1.

Using the simplified in vivo tagging technique, normal subjects were studied in the following manner.

a) Two studies were carried out at several weeks or months interval in 16 subjects. The variation of the rate of plasma iron disappearance was found to be within ∓ 30%. One example is shown in Fig. 4.

b) Three consecutive measurements of plasma iron disappearance rate in 12 hours were carried out in 6 subjects. The variation is within ∓ 30%. One example is shown in Fig. 5.

2. Studies of hemotologic disorders.

Several hundred studies have been carried out in patients with various hematologic disorders. Several cases of special interest merit presentation.

Case 1. S. S. W/F Age 70 #3234-P

History: This patient was found to have pernicious anemia while she was being treated for obstructive jaundice in hospital. Radioiron turnover studies were preformed before specific therapy was instiuted, during vitamin B_{12} therapy when the patient was making a satisfactory recovery, and after complete remission was obtained. The pertinent data from these studies are summarized in Table 2.

Comment: The purpose in presenting this case is only to illustrate the sensitive and precise relation between iron metabolism and disease that can be demonstrated by radioiron studies. Radioiron studies measure two rates: the rate of plasma iron disappearing from the plasma iron pool and the rate of incorporation of iron in the red cells. The first is an indirect and the second

a direct measure of the functional status of bone marrow erythropoiesis. Ordinarily these two rates are parallel. Thus, they are both increased in anemias due to iron deficiency or blood loss and in polycythemia. On the other hand, they are both decreased in anemias due to bone marrow hypoplasia of whatever etiology.

In pernicious anemia, as in the case presented here, the rate of disappearance is increased while the rate of incorporation is decreased. This paradoxical dissociation is a reflection of the basic pathophysiology of pernicious anemia, namely maturation arrest and inability to incorporate iron in the final steps of erythropoiesis.

The remarkable speedy hematologic recovery following vitamin B_{12} therapy is accompanied by the development of a rather marked degree of hypoferremia. As the maturation process is returning to normal, the utilization or incorporation of iron is greatly speeded up. This lowers the serum iron concentration which in turn further stimulates the rate of serum iron disappearance.

When the patient has achieved complete remission with the addition of iron therapy, normalcy of erythropoietic function is reflected by the results of the third study.

From the physiologic point of view, these studies with radioiron have provided information accurately protraying the pathologic distrubances in pernicious anemia and the physiologic adjustment in response to vitamin B_{12} and iron therapy.

Case 2. O. S. Mexican/M Age 15 #CE-9229

This patient was admitted to the hospital with a diagnosis of congenital heart disease involving tricuspid valve and a probable right left shunt. He had intense cyanosis since birth and chronic congestive failure on and off for several years. Hematologic studies revealed a marked degree of secondary

polycythemia. Radioiron study showed markedly increased rate of disappearance, a rapid incorporation of serum iron and a lower plasma iron concentration, consistent with polycythemia. These data are summarized in Table 3 and Figures 6 and 7.

Case 3. M. B. W/M Age 28 #CH-1166

History: This patient was admitted to the polio ward as a case of post-polio hypoventilation syndrome. One year previously he had had acute anterior poliomyelitis with muscular paralysis involving the diaphragm and below. He recovered sufficiently to become ambulatory after 3 months hospitalization and went to Mexico City to live with his sister. As he increased his physical activities there, he soon developed marked cardiac and respiratory symptoms with the findings of severe secondary polycythemia. After 3 weeks treatment, his symptoms gradually subsided, even though the hematologic evidence of polycythemia was unchanged. These are shown in Table 3. The radioiron study performed at this time, 3 weeks after admission to the hospital, seemed at odds with the peripheral blood picture. There was a normal disappearance half time and a markedly decreased rate of red cell uptake. These data are shown in Figures 6 and 7.

The patient continued to improve. His vital capacity increased to 2600 cc. and his polycythemia subsided completely in the course of 6 weeks of observation following the initial studies. These data are also shown in Table 3.

Comment: These two cases of secondary polycythemia are presented together to demonstrate the usefulness of radioiron turnover studies in detecting the distinguishing significant variations in iron metabolism in hematopoiesis. The degree of erythemia in these patients as revealed by the red cell counts and hemoglobin levels is quite similar. Radioiron studies in the boy with cyanotic

congenital heart disease are in order but the findings in the second patient seem quite incompatible with the degree of erythremia which was present. However, the patient had been at rest, at the sea level altitude of Houston, and in a respirator for 3 weeks. The stimulus of anoxia and the demand for increased hematopoiesis had been withdrawn. The normal disappearance half time and the sluggish red cell uptake of serum iron indicate relative inactivity of the bone marrow, even though it was six weeks before the hematologic abnormalities finally returned to normal levels. From a prognostic point of view, the tracer iron study anticipated the eventual recovery six weeks prior to recovery.

These case studies are presented here to show the remarkable sensitivity of the radio-iron study in detecting functional changes of erythropoiesis which generally antedate changes in the numbers of red cells or the concentration of hemoglobin by several weeks as measured by the more conventional methods of study.

3. Studies of cancer patients receiving partial body radiation.

The effects of limited-field roentgen therapy on the plasma iron disappearance rate has been studied in many of our cancer patients treated at the Jefferson Davis Hospital. In these studies, the plasma iron disappearance rate of individual patients was determined before the commencement of radiotherapy and repeated after the completion of the prescribed treatment. The results of these two studies are compared, the pre-treatment data serving as the norm in each individual case.

The data from 38 patients are summarized in Fig. 8. The effect of radiation on plasma iron disappearance half time is expressed as per cent of the norm, or the pre-treatment disappearance half time. This is plotted against the absorbed dose of radiation in megagram-roentgens. A consistent correlation is not found.

4. Studies of cancer patients receiving total body radiation.

Two groups of patients receiving whole body radiation have been studies.

1) In the first group of patients, the plasma iron disappearance rate or half time was determined before whole body radiation was given and repeated on several successive days. The post-radiation changes are expressed as per cent of the pre-treatment half time. This group consisted of 17 patients receiving 200r in 1 treatment, 2 patients receiving 2 treatments of 200r at 3 and 5 week intervals, 1 patient receiving 200r and 100r with 5 weeks interval, 2 patients receiving 5 treatments of 50r, 1 patient receiving 10 treatments of 55r, and 3 patients receiving 100, 125, and 150r respectively. The results are shown in figure 9.

It is apparent that in all except one patient there was a slowing of the rate of plasma iron clearance. The effect appears to be maximal between 48 and 72 hours after the exposure and is followed by a return to normal in about one week.

In this study it was not practicable to measure the maturation time or the rate of red cell uptake, because of the consecutive administration of 3 or 4 tracer doses within 5 to 7 days.

Normally a major portion of plasma iron leaving the plasma pool goes to the bone marrow, and the rate of clearance is for the most part governed by the functional requirement of erythropoiesis. However, the plasma iron pool is also in equilibrium with the storage depots, and plasma iron may be shunted to the liver or spleen at increased rate under certain conditions, such as infectious diseases. Further, as shown in the case of pernicious anemia presented above, the disappearance of plasma iron, while suggestive of bone marrow depression, is therefore not conclusive evidence unless corroborated by parallel changes in red cell uptake.

2) In the second group of five patients the effect of whole body radiation upon the uptake of tracer iron by red cells was investigated. These patients received 100r at one session. Because of the transient depression occurring between 2 - 3 days after radiation demonstrated in the first series of experiments, the radioiron study was carried out around this time. The red cell uptake was repeatedly determined in a period of two weeks following administration of the tracer. The results are shown in Fig. 10. The total uptake was not affected. The maturation time was likewise within normal limits.

Comment: Several possible explanations may be offered for these negative results.

1. With the amount of radiation (100r) given to these patients, there may have been no effect on iron metabolism or erythropoiesis.

2. The effect of radiation may not have developed during the period of observation - 2 weeks post-radiation. The short term observation was chosen in an attempt to detect if there was any functional abnormality in an early phase before the development of recognizable anemia. For total body radiation of the order of 100r, no early effect is apparent in utilization of iron in red cell manufacture.

3. Factors other than dose and timing may influence or obscure the effects of whole body radiation on iron turnover patterns for patients with advanced malignant diseases and various complications. Many of these patients have varying degrees of malnutrition, anemia, or insufficiencies in hepatic, renal, or cardiac functions which may be subclinical and difficult to evaluate. Their total influence on erythropoiesis (or any other body function) may be appreciable but seldom quantitatively measurable in a controlled manner.

III. Effect of Irradiated Blood on Hematopoiesis

1. Irradiation of blood in extra-corporeal circulation.

This procedure was described in the report submitted for the period ending September 1, 1957.

In the course of studying the effects on circulation in the dog, of heart-lung preparation, advantage was taken of the opportunity to irradiate intensively the blood of the animal as it was circulated outside the body. In 10 animals so studied the white blood cell count showed an initial depression during the first 2 hours, followed by recovery and elevation beyond normal for some weeks. This prolonged elevation was not seen in animals subjected to trauma of the extra-corporeal circulation without irradiation.

2. Transfusion of plasma of 5 dogs previously subjected to extra-corporeal irradiation of blood into normal dogs.

Five dogs were subjected to irradiation of blood in extra-corporeal circulation. Blood was withdrawn by cardiac puncture into glass transfusion bottles containing 120 cc. of A.C.D. anticoagulant and stored in refrigeration until used. The plasma was separated by centrifuging and withdrawing by vacuum into 250 cc. plasma transfusion bottles. This plasma was then given intravenously into 5 normal dogs and observations made on white blood cell count, red blood cell count and hemoglobin over a period of 150 days.

The white blood cell count showed an immediate depression (Fig. 11) followed by a rather erratic rise beyond pre-treatment levels. A longer period of observation before transfusion might indicate whether the observed fluctuations were significant but the first impression is that no clear effect on white blood cell count resulted from transfusion with plasma of dogs who received extra-corporeal blood irradiation.

The response of red blood cell count (Fig. 12) and hemoglobin (Fig. 13) showed a change that was sufficiently consistent, marked and prolonged to merit close study. All dogs showed an elevation of red blood cell count of 20 to 100 per cent, and of hemoglobin of 15 to 30 per cent above pre-treatment levels persisting for a period in excess of 3 months.

When these dogs had been under observation for 24 to 69 days after receiving the transfusion of plasma, radioiron turnover studies were done.

Two control dogs		Disappearance half time	Incorporated into RBC 8 days	14 days
#1		38 min.		
#2		41 min.		
five dogs receiving plasma from extracorporeally irradiated dogs.				
#1	24 days after Rx	92 min.	72.4%	74.5%
#2	40 " " "	57 min.	74.4%	83.3%
#3	40 " " "	70 min.	80.9%	81.2%
#4	66 " " "	57 min.	91.8%	94.4%
#5	69 " " "	58 min.	85.4%	93.3%

The prolonged disappearance half time in association with a persistent elevation of red blood cell count and hemoglobin resembles the picture encountered in patients recovering from a secondary polycythemia.

3. Transfusion with irradiated plasma in normal dogs.

For reasons of convenience, observations were made to determine whether simple withdrawal of blood, irradiation of the withdrawn blood and transfusion into a second dog of the separated plasma would produce a similar elevation of red blood count and hemoglobin values.

The steps in the procedure were:

1) Cardiac exsanguination

2) Irradiation of the withdrawn blood to 10,000r

3) Separation of plasma after 24 hours

4) Transfer of irradiated plasma to a second normal dog.

The results of this procedure in 3 dogs is shown in figures 14, 15 and 16. The red cells and hemoglobin values again show consistent elevations persisting for over 3 months.

4. Autotransfusion with irradiated whole blood in normal dogs.

The procedure here was as follows:

1) Arterial blood withdrawn by cannula from femoral artery

2) Immediate irradiation of withdrawn blood to 15,000r (20 minutes irradiation)

3) Autotransfusion begun within one hour of initial withdrawal of blood.

One of these animals (#9) lost 200 cc. of blood when the arterial cannula was dislodged and autotransfusion was carried out with 320 cc. of irradiated blood. There was an initial fall of red blood cell count within the first 24 hours, followed by a rise (13% above pre-treatment level) at 3 days, with a gradual return to normal at 5 weeks. The initial fall in hemoglobin at 24 hours was followed by a rise to 5% above pre-treatment level at 48 hours, with a gradual return to normal at 5 weeks. The second dog (#10) showed a marked elevation of red blood cell count and a persistent slight elevation of hemoglobin above pre-treatment levels. These data are shown in figures 17, 18, and 19.

5. Autotransfusion with irradiated whole blood in human cancer patient with microcytic anemia.

Case 4. B. B. C/M Age 71 #DE-3369

History: This patient first came to the hospital in 1956 complaining of

swelling of his abdomen. He was found to have a filling defect on the greater curvature of the stomach, presumed to be a neoplasm. Peritoneal fluid showed probably malignant cells and a mass could be felt through the abdominal wall.

Radiation therapy:

October 25, 1956 - 100 mc. radiogold instilled in peritoneal cavity.

February 28, 1957 - 100r total body radiation (rotation technic, 2 MeV Van de Graaff).

July 30, 1957 - 148 mc. radiogold instilled in peritoneal cavity.

January 30, 1958 - 500 cc. of patient's blood was withdrawn under sterile conditions; the blood was irradiated by the Van de Graaff machine to a level of 5,000r (measured at surface of the blood in the container). The blood was then re-transfused to the patient.

Clinical course: Following the first instillation of radiogold in the peritoneal cavity, the patient did not require paracentesis for five months. After receiving 100r total body radiation, there were no untoward symptoms, the hospital course was uneventful and he was discharged 3 days after treatment. The pre-treatment level of white blood count ranged from 5,000 to 7,000 per cubic millimeter; after total body radiation it was 3,000 to 5,000. Fluid gradually re-accumulated and the patient required further paracentesis. The second administration of radiogold had much less effect in accumulation of ascitic fluid than the first instillation. In September 1957, the patient was admitted to hospital and an exploratory laparotomy was done. Biopsy of peritoneal seedings showed mucinous carcinoma, probable site of origin in colon. Following this, there was again slow accumulation of ascitic fluid but he did not require paracentesis.

In the six months prior to the autotransfusion, his hemoglobin had not been recorded above 9.9 gms. per cent and was 7.7 gms. per cent at the time of transfusion. After transfusion, his hemoglobin rose to 10 gms. per cent in 12 days and his white blood cell count rose to the genral level between 5,000 and 7,000 per cubic millimeter. His red count varied between the pre-treatment levels of 3,560,000 to 4,200,000 during the two weeks following transfusion. By the time one month had elapsed, the hemoglobin had fallen back to 9.3 gms. per cent and the white blood count had again fallen to the previous level of 3,000 to 5,000 per cubic millimeter (Fig. 20).

Comments: The prompt rise of 3 gms. per cent of hemoglobin, and of the white blood count to original levels for the first time in over a year, merits further study. This may well be a non-specific reaction associated with autotransfusion procedure or it may be a response to an altered plasma fraction as a result of irradiation. There is need to compare the effect of unirradiated autotransfusion. If further autotransfusions to human subjects sustain the interest in this effect, plasma electrophoresis or assay of the various plasma fractions can help to isolate the responsible factor.

IV. Lethal Total Body Radiation in Dogs.

Purpose: To find a uniformly lethal dose of irradiation in dogs which could be relied upon to destroy completely the bone marrow for the subsequent purpose of giving heterologous bone marrow transplants.

Materials: Dogs were selected in the weight range of 8 to 14 kilograms. Bone marrow and peripheral blood specimens were obtained before irradiation and the dog was then given total body radiation on a rotating platform with the 2 MeV Van de Graaff. The dogs were then subjected to bone marrow and peripheral blood tests immediately following radiation and at 24 hour intervals for the remainder of life.

Dosage: The first group of 3 dogs were given 150r, 450r and 600r respectively (2 MeV irradiation, inherent filtration, 6.8 mm Pb., treatment distance 3 meters, Hvl. 20 cm. tissue). At ten days all were alive and only the one with 600r showed evidence of the irradiation. This was manifest by a gross bleeding tendency around the gums and tongue and a failure to heal with slough of an area of hematoma on the left hind leg at the site of the vena puncture. This dog was sacrificed on the eighth day and still showed active bone marrow. The other two dogs remained well. The one receiving 150r was discarded. The dog with 450r was sacrificed on the 9th day and the spleen and adrenal glands were sent for sections as yet unreported.

The second group of three dogs were all given 1,000r. One of these died during anesthesia. The other two died within 3-4 days of intercurrent infection. The bone marrow and peripheral blood counts on these dogs showed only minor deviation downward within the period of their lives. At death there were still many forms of apparently viable cells in bone marrow. It was felt, however, that the dose of 1,000r was too high.

The seventh dog received 800r in the same manner with factors as follows: 2 MeV radiation, inherent filtration 6.8 mm. Pb., treatment distance 2 meters, Hvl. 20 cm. tissues, delivery rate 17r per 100 metered. This dog lived 9 days.

Bone marrow findings can be summarized as follows:

1. Almost immediate disappearance of all lymphoid elements within two days of total body radiation.
2. Gradual diminution in the granulocytic elements and erythroid elements to the time of death.
3. Evidence of remaining active blood forming cells at the time of death.

Comments: Death of all the animals seemed to be a combination of hemorrhage and infection. These animals were not given antibiotics during the course of the study so as not to preclude any clouding of the results.

Although there were active blood forming cells found at death, these may well be non-viable ones soon to die. With the bleeding and infection, death may have occurred before actual aplasia of the marrow. In further observations on lethal doses of total body radiation, an attempt will be made to sustain the animal by antibiotics and supportive treatment so that maximum depression of bone marrow can be observed.

There was one further dog irradiated with 800r (rotation method, 2 MeV radiation, inherent filtration 6.8 mm. Pb., treatment distance 2 meters, Hvl. 20 cm. tissues). Results in this dog compare in all but two respects with the previous dog. 1) The drop in white count was not evident until after the first day following irradiation but fell to 133 at the time of death on the 10th day. 2) There was no evidence of immediate rise in platelet at the end of treatment. The elevation in hemoglobin and red count, and the duration, were the same as the previous dog. Response of both animals is illustrated in Figure 21.

V. Clinical Observations on Patients Receiving Total Body Radiation.

In reviewing records of patients who have received total body radiation, there have been instances where the effect of an amount of radiation, believed well within the limits of tolerance, has been excessive or augmented by other factors. The question whether this is an inherent difference in sensitivity or resistence to radiation or whether this is the result of concomitant disease or constitutional condition which increases the sensitivity to radiation remains unanswered in most cases. Two examples of this are outlined in detailed case histories.

Case 5. I. S. W/M Age: 85 #AE-8241

History: This elderly but vigorous independent farmer had a submandibular mass for about one year before it was finally diagnosed as lymphosarcoma, lymphocytic type on October 18, 1956. By this time he had developed a generalized lymphadenopathy; bone marrow studies were within normal limits and showed no lymphosarcoma. His hemoglobin was 10.3 gm. per cent, WBC was 4,000 at this time. Because the patient had to travel some 40 miles to get to the hospital, driving himself in a farm truck, his treatment schedule was somewhat irregular.

Radiation therapy: October 30 - November 9, 1956 - Local treatment to the right inguinal region and to the left axilla, 350r skin dose to each site (250Kv radiation, Hvl. 3.2 mm., Cu., field size 10 x 15 cm.). January 14 - July 22, 1957 total body radiation, 241r total. This was given in 17 treatments of 10 to 20r each (the first 3 were 10.5r each and the last 8 were 10.5r each and the other 6 were 21r each), irregularly spaced through this period. (This total body radiation delivered at 220 Kv., Hvl. 1 mm. Cu., treatment distance 300 cm., output 1 r per minute. The dose was measured at the surface of the patient, incident radiation plus backscatter). During the interval of his total body irradiation, he received 2 single treatments; one of which was to the right

inguinal region, through an 8 x 12 cm. field, 282 r tumor dose in a single treatment. The other was to the left submandibular area through a 10 x 15 cm. field, 700 r tumor dose in a single treatment. The relationship of the blood counts to treatment throughout this period is given in figure 22.

Clinical course: The palpable lymphadenopathy always responded quite readily to radiotherapy throughout the entire time of his treatment. The hemoglobin remained at near normal levels until late July 1957 when it began to fall. The platelet count remained normal until August 1957 and it then began to fall. The differential count of the white blood cells remained about 50 per cent lymphocytes and 50 per cent segmented cells until his last admission when the cells became predominately lymphocytes and of those, the predominate cell was the lymphoblast.

He was admitted twice for transfusions, once in August, 1957 and again in October, 1957. During his last admission from November 18, 1957 to December 8, 1957, he received 4 transfusions and was on Meticorten, 10 mg. every 6 hours. During his last admission, his white blood cell count began to rise and reached the level of 20,000 at the time he expired. Bone marrow studies on the day before death showed many lymphoid cells, few granulocytic cells and no erythroid precursor cells.

Post-mortem examination on this patient showed the followings 1) lymphosarcoma, lymphocytic type, 2) lymphatic leukemia, chronic, 3) leukemic infiltration of the liver, spleen and kidneys, 4) hypoplastic anemia. Representative samples of each of the tissues from this man's post-mortem examination have been sent to the Armed Forces Institute of Pathology to Col. Carl Tessmer for examination.

Comments This elderly man with clinically evident lymphosarcoma diagnosed on tissue specimens, with obvious palpable nodes and no particular symptoms or any discomfort which kept him from his normal activities except for the final anemia which brough him to the hospital on his last admission. Except for the abnormally low constant level of his white blood count, he retained a normal blood picture throughout until the terminal anemia. He was treated with total body radiation in divided doses and localized radiation to enlarged lymph nodes over a period of 8 months. He developed a hypoplastic anemia and a picture of lymphocytic leukemia at the time of his death which was clinically of the acute type and at post-mortem examination showed the histological behavior of a chronic leukemia. The major possibilities for this picture are

1) End stage lymphosarcoma with the picture of a so-called leukosarcoma.

2) Chronic lymphocytic leukemia which remained aleukemic until the terminal stage and then became acute in behavior. This is quite a normal course for chronic lymphocytic leukemia whether the patient receives chemotherapy or radiation therapy, or no therapy.

3) Irradiation produced mutation in the usual course of lymphosarcoma manifesting itself as leukemia in the final stages.

The evaluation of effects of radiation in the blood dyscrasias and lymphomas is most difficult when the major marker is the blood count itself. This will vary with both irradiation and with the primary disease. In regard to the terminal anemia that this man had, this also is seen in both the terminal phase of blood dyscrasias from crowding of the bone marrow and in total body radiation but at higher levels than this man received.

Case 6. B. P. C/M Age:59 #115449

History: This muscular rice warehouse worker complained of shortness of breath for 6-7 weeks and left chest pain for 3-4 weeks. Left upper lobe pneumonia was diagnosed on 3/22/57 and treated with antibiotics. He was discharged from hospital on the fifth day after admission. He was readmitted with recurrence of cough and chest pain on 4/1/57. The area of consolidation of the left upper lung field had increased and cavitation had developed. A diagnosis of squamous cell carcinoma of the lung was made by needle biopsy on 4/10/57 and the patient was referred for radiotherapy.

Treatments: 4/15/57 - 150r total body irradiation (2 MeV x-ray, rotation method, dose measured in air and axis of rotation, 4.4 megagram roentgens integral dose). 4/17/57 - 4/22/57 - 1200r tumor dose delivered to a lesion in the left upper lung field (opposing 15 x 15 cm. fields, 250 Kv radiation, Hvl. 2.2 mm. Cu., integral dose 5.4 mg/r).

Clinical course: Following total body radiation, there was no malaise, nausea or symptoms of any kind. The patient was transported by ambulance between the hospital and the building housing the 2 MeV Van de Graaff. He was under close observation for a period of three hours following radiation. The exposure was over a period of 40 minutes, from 3:00 to 3:40 p.m. He ate a normal hospital evening meal at 5:30 p.m. and slept soundly through the night without medication of any kind. On the first post-radiation day, no change in his condition could be observed. He reported no untoward symptoms, his appetite was normal and he was up and about hospital ward as he had been prior to radiation.

On the second hospital day following total body radiation, local therapy to the carcinoma of the lung was begun and he received a daily dose of 200r during the next week as above described. He showed no change during this period. He tolerated treatment well without neausea and with no change in strength or appetite. Treatment was interrupted at this time in accordance with a policy

of awaiting the effects of initial treatment so that clearing of pneumonia and regression of tumor would permit more precise localization; the use of smaller treatment fields and the treatment of a smaller volume of tissue.

On May 1, 1957, while still in hospital, he first showed cerebral symptoms and stiff neck. The first clinical suspicion was cerebral metastases and on May 2, 1957, an electroencephalogram was made but this was normal. The clinical symptoms of meningitis developed and this was now associated with leukopenia and thrombocytopenia as shown in Figure 23. There were no electrophoretic studies done on the plasma protein fractions throughout his entire hospital and clinic visits. Treatment by antibiotics for the meningitis and by transfusion and Cortisone for the leukopenia and thrombocytopenia did not alter the clinical signs or symptoms. No bleeding tendency developed. He became terminal and died on May 12, 1957.

Post-mortem showed a purulent meningitis, bilateral bronchial pneumonia, squamous cell carcinoma of the lung and bilateral adrenal atrophy. Tissue blocks from this post-mortem examination has been sent to Col. Carl Tessmer of the Armed Forces Institute of Pathology for study.

Comment: The importance of this case lies in its bearing on the concept of minimal lethal dose. The 150r total body radiation that this patient received and the additional 1200r tumor dose (delivered to the site of the primary lung cancer) were not considered as an amount of radiation that would even approach the local or systemic tolerance level. The plan of treatment based upon our estimate of normal tolerance would have been to add at least an additional 3,000r tumor dose to the primary lung cancer. The falling white and platelet counts first noted on May 1, 1957 was at first surprising but not alarming. The interpretation of cerebral symptoms as probable cerebral metastases distracted attention from the possible significance of leukopenia indicating a

hazard of infection. On recognition of the infection, an intensive regime of antibiotic therapy failed to control his complication which was the cause of his death.

There are four possible interpretations here:

1. The amount of radiation the patient received represents a minimal lethal dose and that death is a direct result of radiation.
2. The patient did have a dysgammaglobulinemia and the susceptibility to infection which with the added stress of radiation, was responsible for the train of events leading to his death.
3. The patient, having an overwhelming infection such as pneumococcus meningitis linked with the effect of total body radiation, manifested the extreme leukopenia which indicated his very poor resistence to the infection and therefore resulted in his death.
4. This patient suffered from a disorder manifested as a dysgammaglobulinemia, a low resistence to infection which was the participating factor in the terminal meningitis, and that the association with the partial course of radiation was coincidental. The question cannot be settled for this case.

The bearing of this study to tolerance to radiation is to indicate that when very large numbers of the population are subjected to radiation as in the event of the atomic disaster, we must be prepared to accept a very low amount of radiation as the minimal lethal dose, even less than 100r. This is because there will be individuals with either manifest or occult competing disease whose demise will either coincide with exposure to radiation or may be hastened by or ascribed to radiation.

The maximum lethal dose will not be altered by the presence of ill or vulnerable individuals in the radiated group and there are no known factors other than an error in dosimetry which would increase the value by which one

might estimate the maximum lethal dose.

The LD 50 will be diminished by factors depressing the minimal lethal dose and it is doubtful if any estimate expressed as a single value has worthwhile meaning unless the spectrum of health and disease in the radiated population can be closely appraised.

CONCLUSION AND FUTURE

1. The dosimetry of radiation exposure is of particular importance for the comparison of technics in different institutions, for the comparison of clinical and laboratory observations and for relating radiation effects under these circumstances to those which might be encountered under field conditions. It should not be anticipated, however, that ever increasing precision of physical measurements will contribute importantly to the study until the biologic response to radiation can be measured with equal precision. This is not to say that physical measurements are unimportant by any means. The care with which they are recorded will permit duplication of the conditions of radiation exposure in different institutions and will permit the re-evaluation in the future should a change in biologic measurement become available.

2. In the attempt to find a quantitative relation between physical dosimetry and biologic response to radiation, iron metabolism and hematopoiesis have been studied extensively. At levels below 200r total body radiation in a single exposure, some interference is detected with the disappearance of injected radioiron, but the utilization is not altered in any usefully sensitive degree. This is at odds with the findings of Hennessy and Huff who detected changes in rats at levels as low as 25r. This basic work must be repeated.

Gastro-intestinal function may lend itself to quantitative estimation of injury. The sensitivity of the gastro-intestinal mucosa is well documented from symptomatology of radiation sickness and by pathologic studies of gross and

microscopic studies. Several radioactive tracers have in recent years been employed in measurement of gastro-intestinal absorptive capacity. These are I-131 labeled serum protein (RISA), I-131 labeled fat and fatty acids, and Co-60 labeled vitamin B_{12}. We propose to study a series of patients receiving whole body radiation or large abdominal field radiation therapy. A pre-treatment test will serve as control of subsequent studies to be carried out at different intervals after the radiation exposure.

3. The availability of a heart-lung preparation used in cardiac surgery made possible the study of intensive radiationof blood in extra-corporeal circulation. One observation was that when plasma from dogs so irradiated was given to normal animals, this was followed by a sustained rise in hemoglobin and a radioiron picutre suggestive of a secondary polycythemia. This bizarre reaction has been duplicated and appears to merit further study.

4. Studies have been begun on lethal dose of total body radiation in dogs. The purpose here is to develop experience in technics of marrow transfusion in preparation to extending this observation to primates.

5. Continued observations on human patients receiving total body radiation emphasize that the minimal lethal dose that may be ascribed to radiation will be lowered by the presence of concomitant disease. The presence of occult factors which might be responsible for increased susceptibility to infection or undiagnosed anemia might lead to complications and death associated with levels of total body exposure of 100r or less.

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30	

Table 1

A comparison of Plasma Iron Disappearance Half Time and Plasma Volume measured by the *in vivo* vs the *in vitro* tagging technique

Patients	Disappearance Half Time in minutes		Plasma Volume in ml	
	in vivo	in vitro	in vivo	in vitro
ds	37	37	1740	1790
rm	83	80	3200	3120
mm	84	84	2100	2160
oc	38	38	2300	2100
ds	42	42	1700	2160
he	76	67	3100	2960

Table 2

Case 1. S.S. 70-w-f. Severe pernicious anemia. Good response to vitamin B_{12} therapy. Developed hypoferremia, which responded to oral iron therapy.

	Before Therapy	During B_{12} therapy	Maintenance B_{12} plus oral iron
	Oct 55	Mar 56	Sept 56
Hemoglobin (gm%)	4.9	10.2	17.2
Reticulocytes (%)	0.7	16.3	1.1
Serum iron (ug%)	163-176	33-38	172-182
Fe^{59} Disappear T/2 (min)	32	20	102
Red cell uptake (% in days)	21 in 14	77 in 4	67 in 5

Table 3

Secondary Polycythemia

	Case 2	Case 3	
	congenital heart	Post-polio hypoventilation	
		2-8-56	3-21-56
Vital capacity ml		1100	2600
Hemoglobin gm%	17-19	18-20	14.4
Hematocrit %	60-70	70-80	46.0
Serum iron ug%	60-65	300-350	-

Fig. 1. 220 Kv.

ABSORPTION IN TISSUE EQUIVALENT MATERIAL

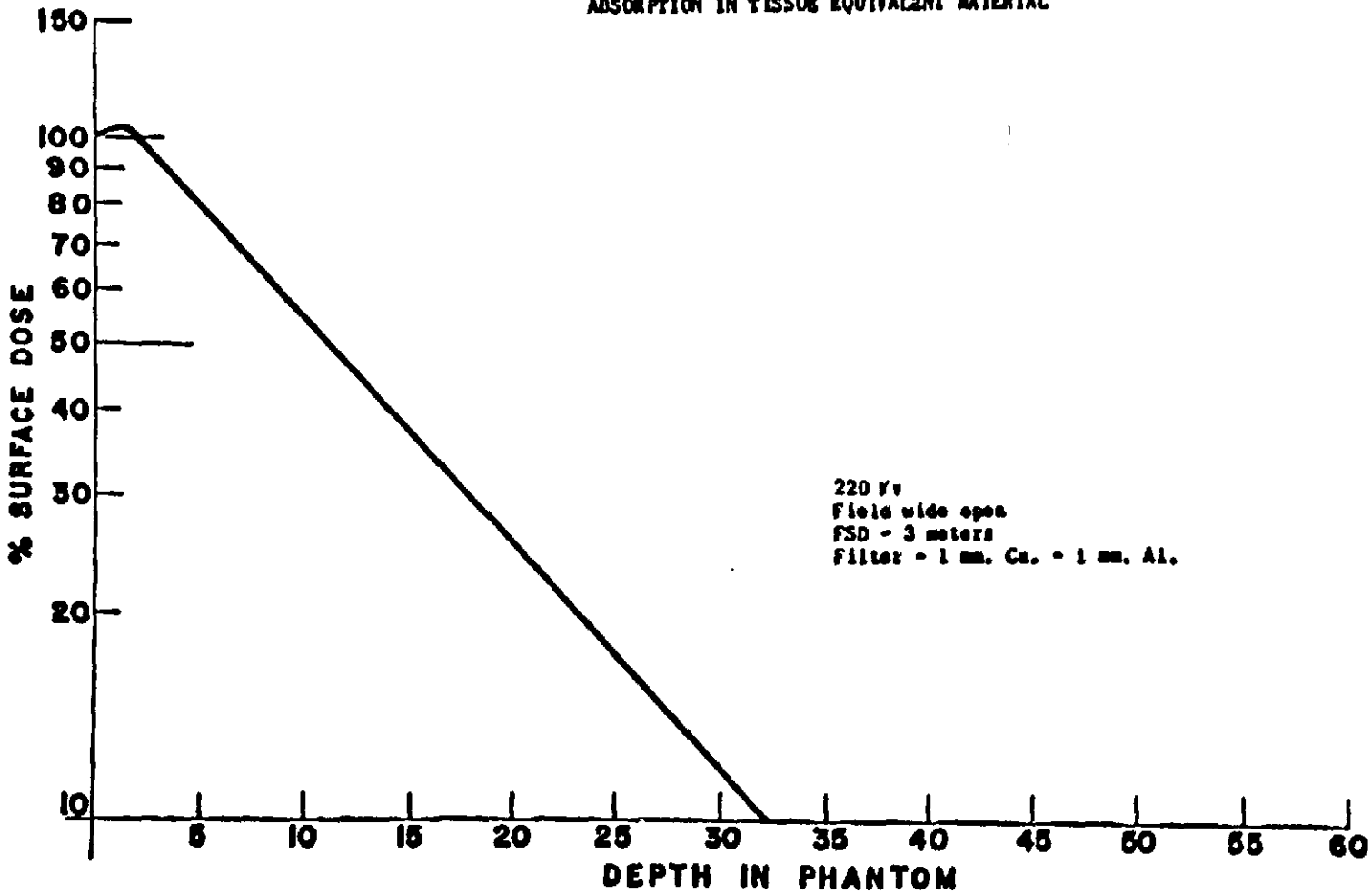


Fig. 2 Absorption ABSORPTION IN TISSUE EQUIVALENT MATERIAL

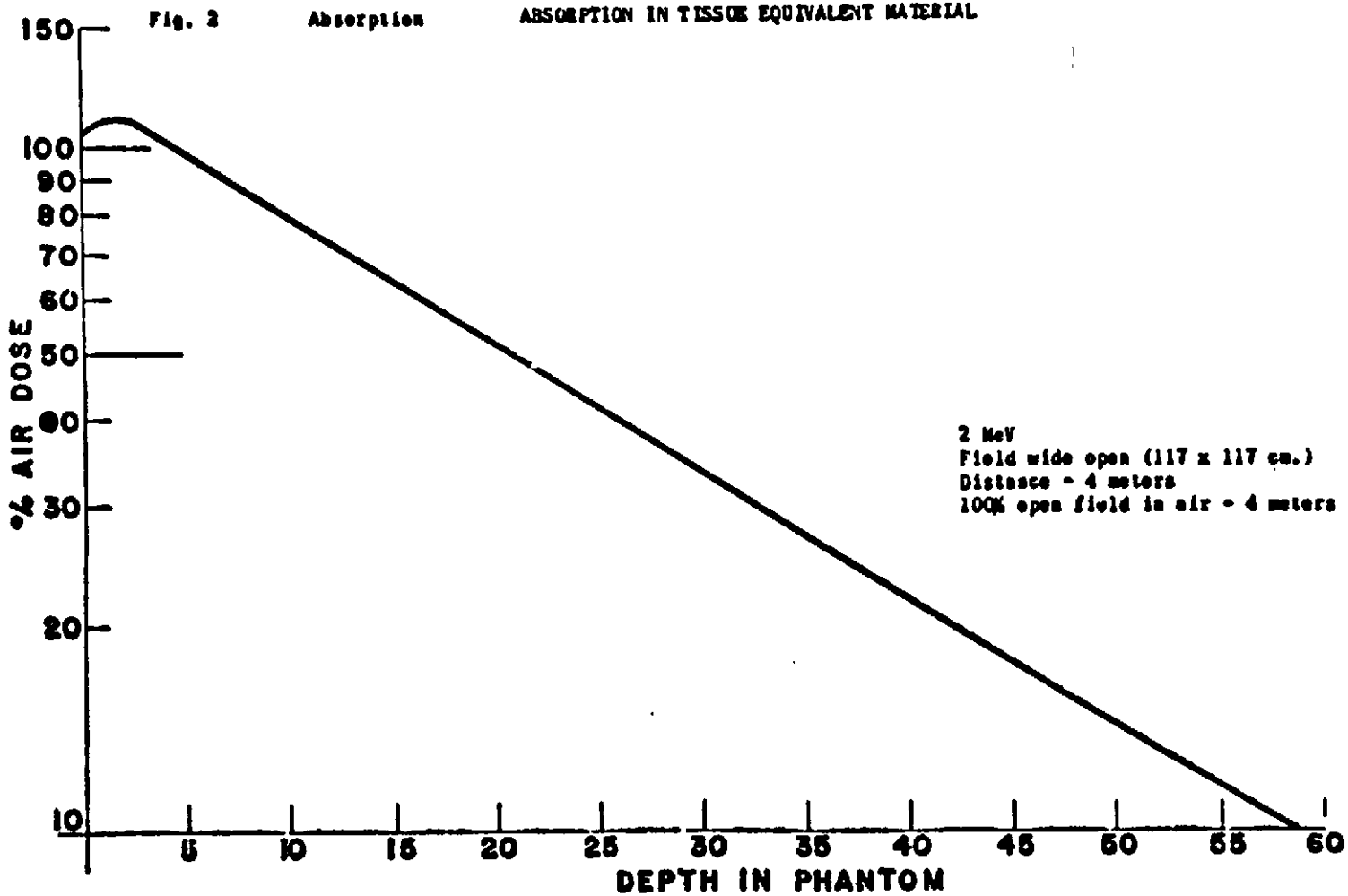


Fig. 3 INTEGRAL DOSE

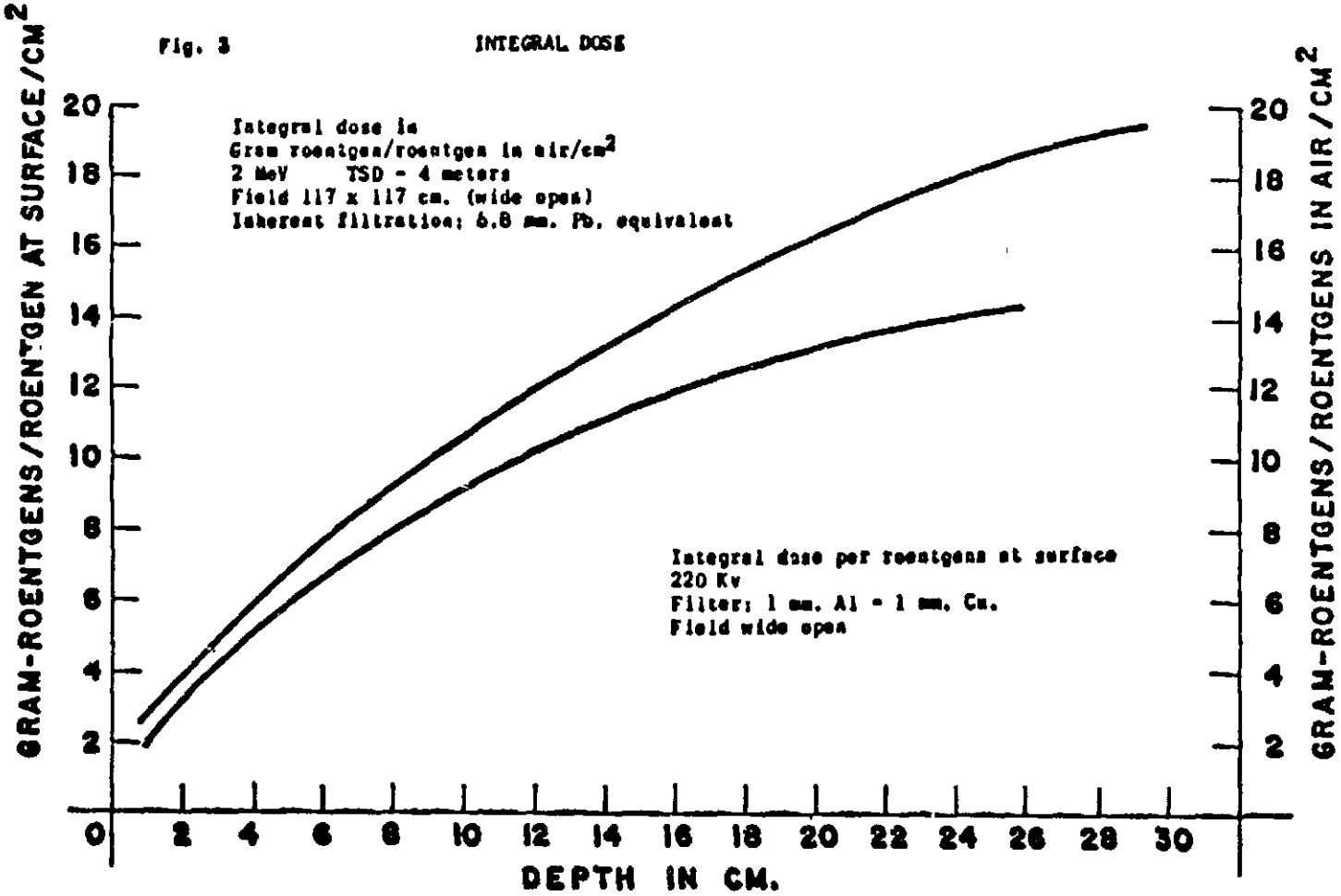


Fig. 6 DISAPPEARANCE OF PLASMA Fe^{59}

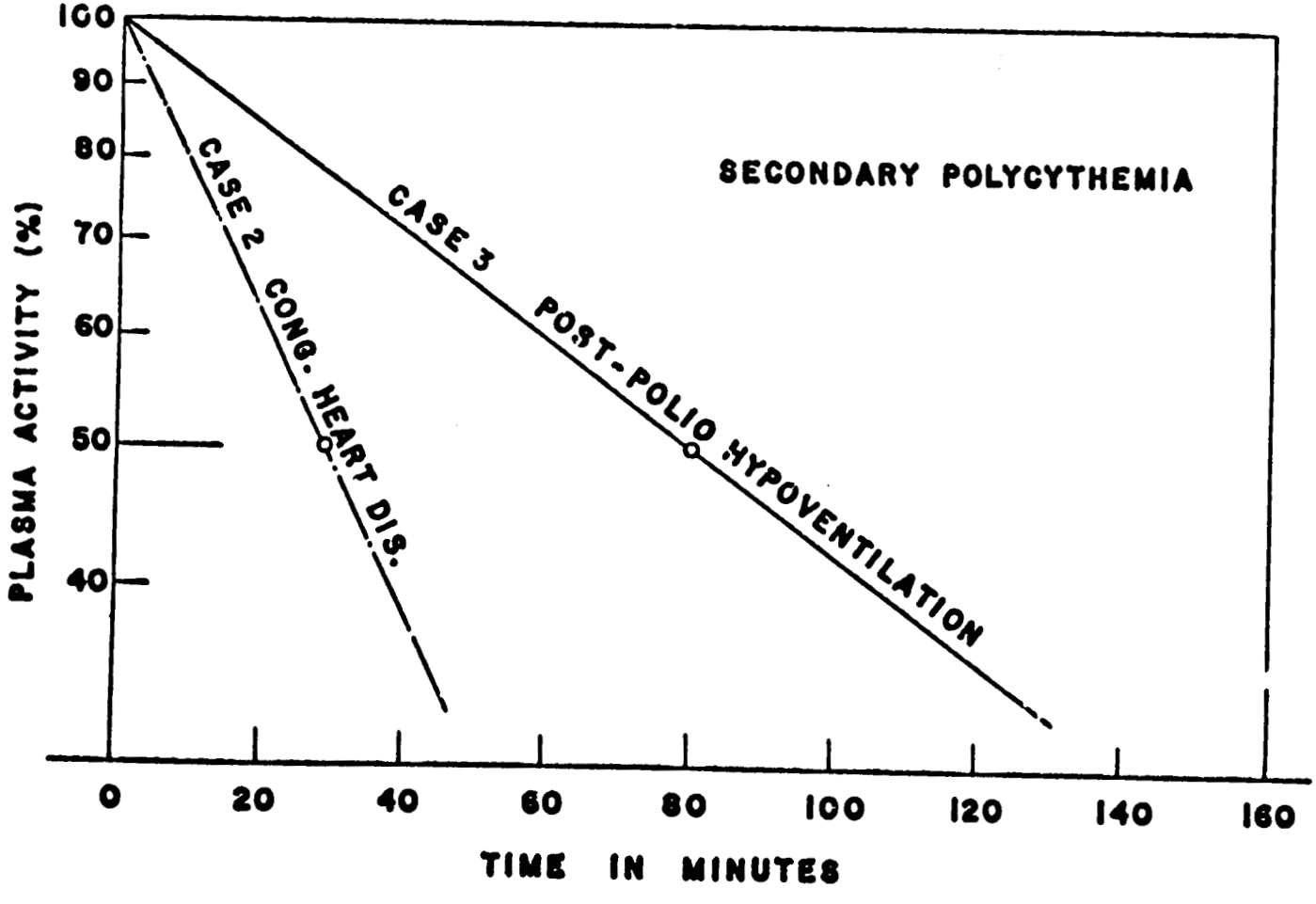


Fig. 6 DISAPPEARANCE OF PLASMA Fe^{59}

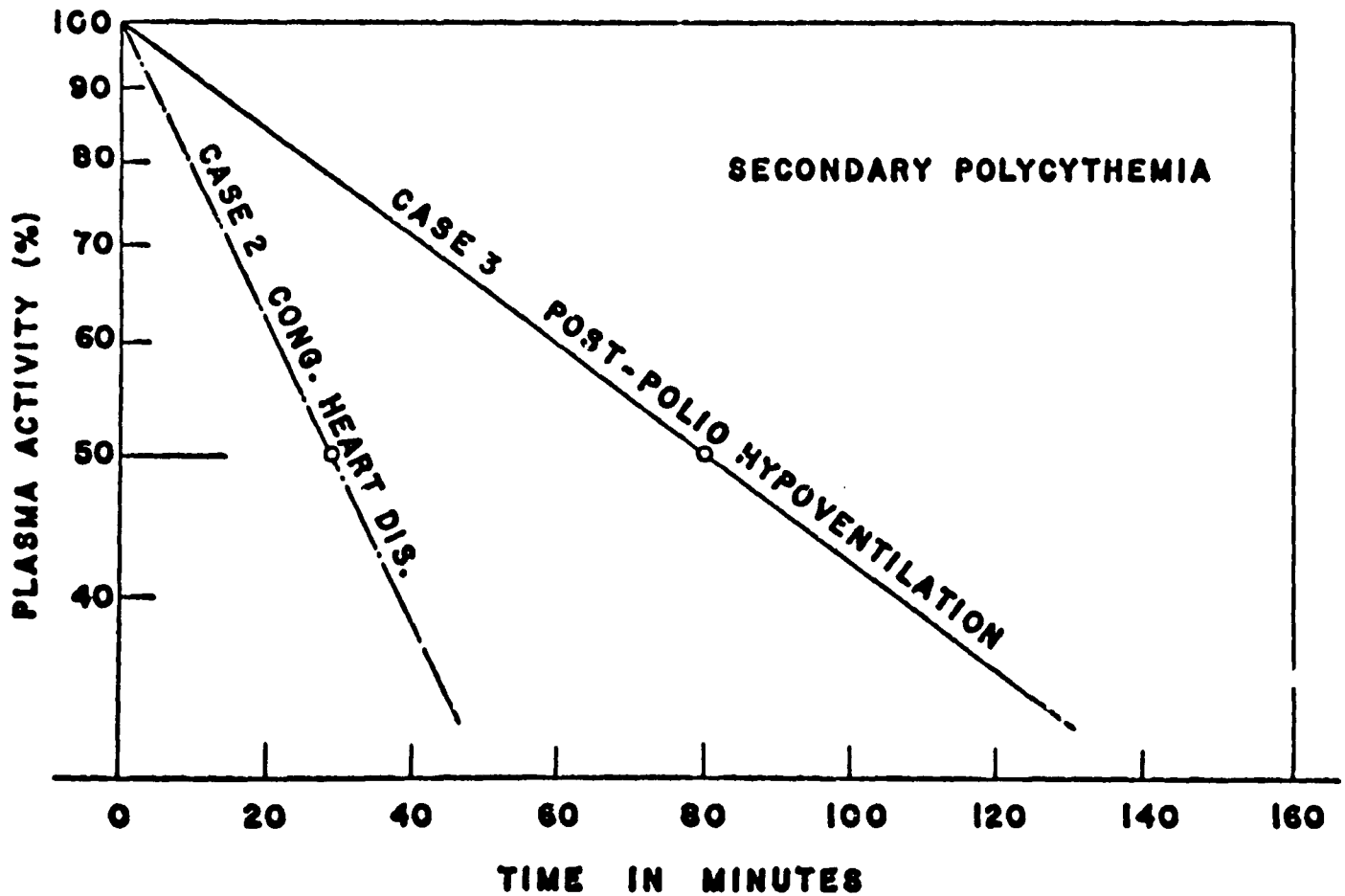


Fig. 7 INCORPORATION OF Fe^{59}

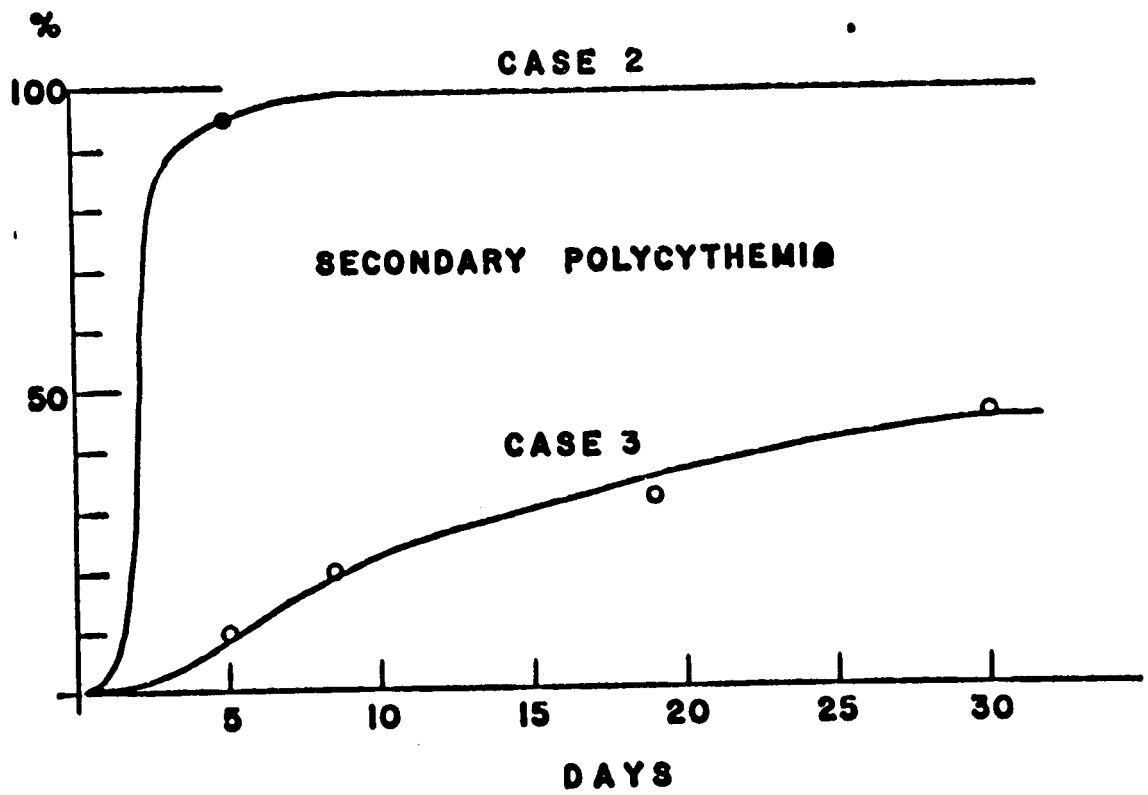


Fig. 8

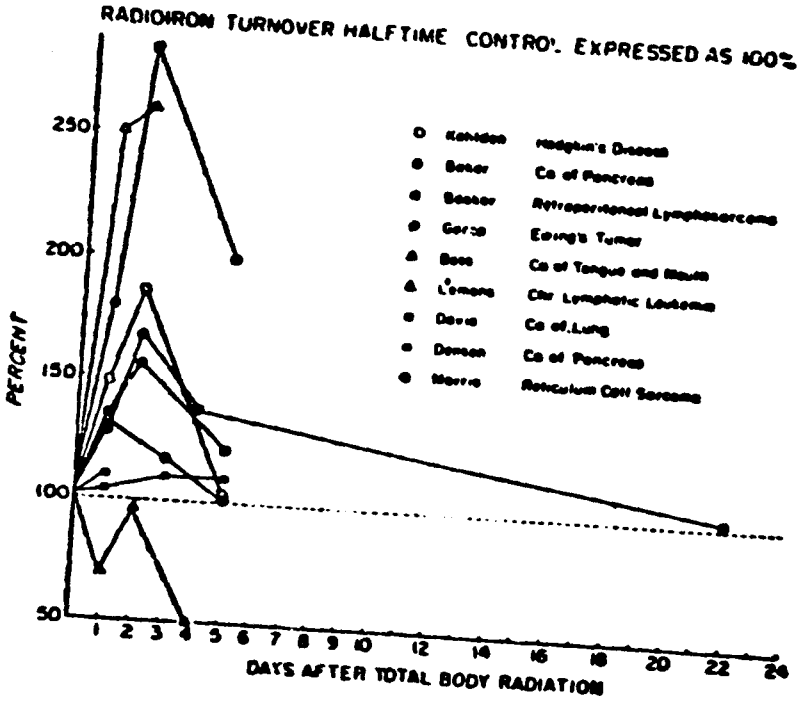

RADIOIRON TURNOVER HALFTIME CONTROL EXPRESSED AS 100%
PERCENT
250
200
150
100
50
1 2 3 4 5 6 7 8 9 10 12 14 16 18 20 22 24
DAYS AFTER TOTAL BODY RADIATION
Hodgkin's Disease
Ca of Pancreas
Retroperitoneal Lymphosarcoma
Ewing's Tumor
Ca of Tongue and Mouth
Chr Lymphatic Leukemia
Ca of Lung
Ca of Pancreas
Reticulum Cell Sarcoma

Fig. 9

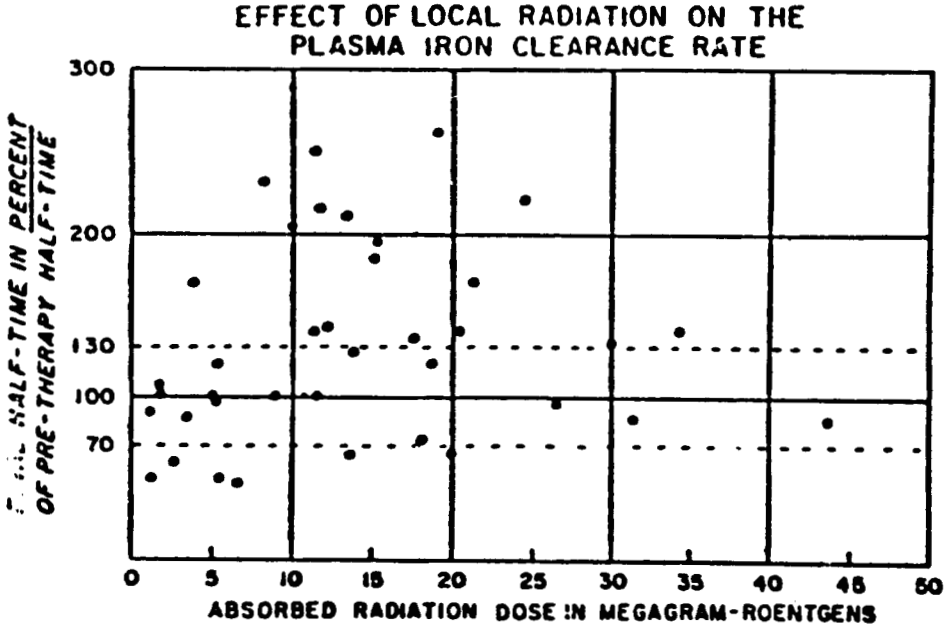

EFFECT OF LOCAL RADIATION ON THE
PLASMA IRON CLEARANCE RATE
300
200
130
100
70
HALF-TIME IN PERCENT
OF PRE-THERAPY HALF-TIME
0
5
10
15
20
25
30
35
40
45
50
ABSORBED RADIATION DOSE IN MEGAGRAM-ROENTGENS

Fig. 10

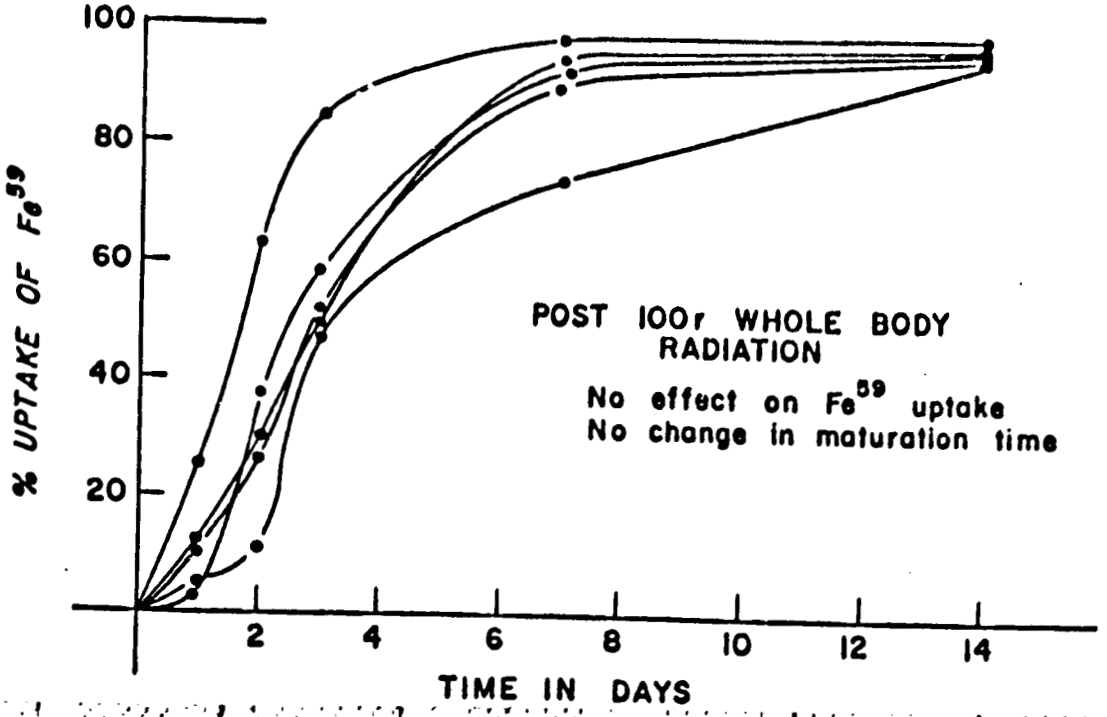

100
80
60
40
20
% UPTAKE OF Fe^{59}
2
4
6
8
10
12
14
TIME IN DAYS
POST 100r WHOLE BODY RADIATION
No effect on Fe^{59} uptake
No change in maturation time

Fig. 11 TRANSFUSION OF EXTRACORPOREALLY IRRADIATED PLASMA

Effect on White Blood Cell Count in 5 Dogs

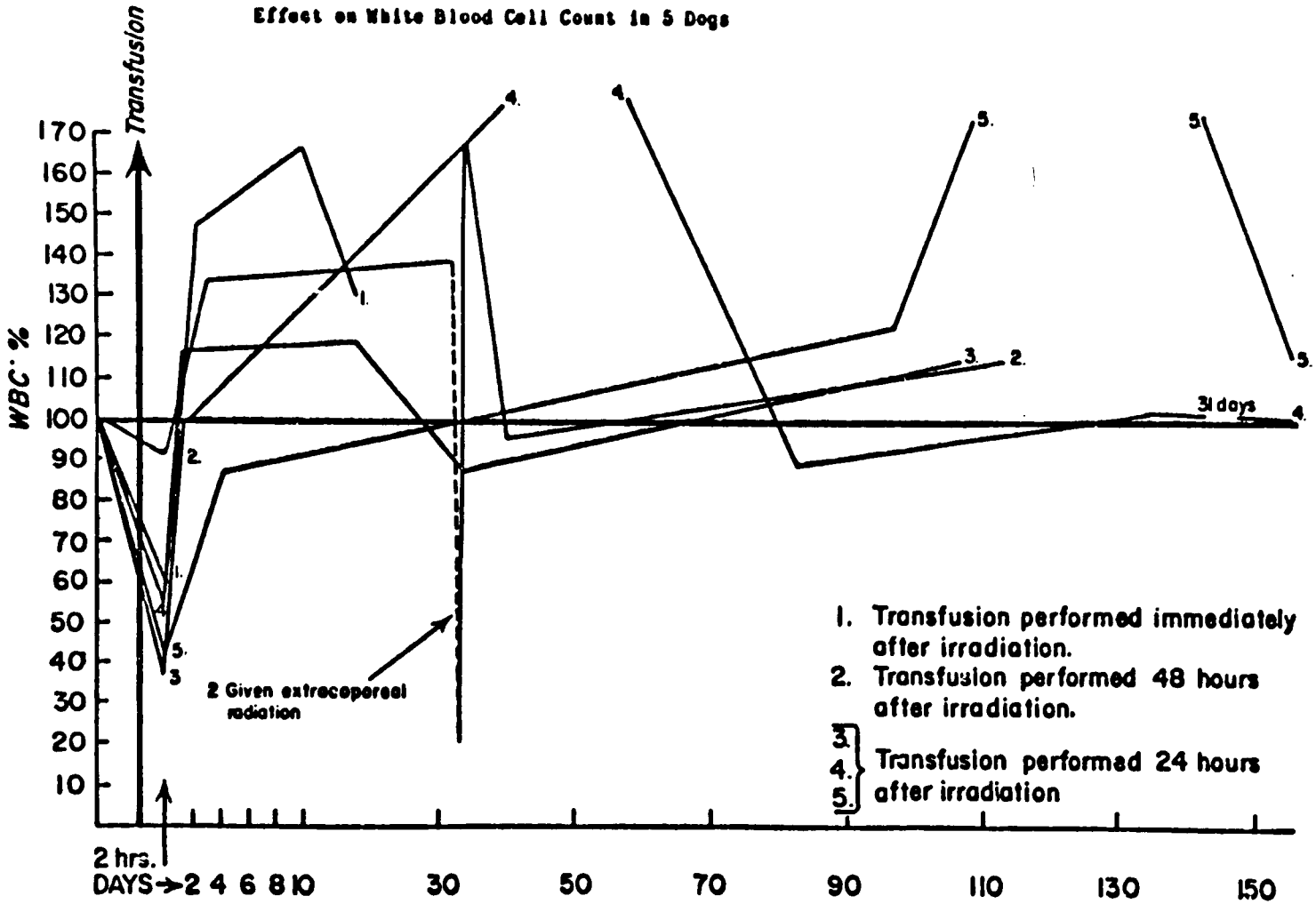


Fig. 12 TRANSFUSION OF EXTRACORPOREALLY IRRADIATED PLASMA

Effect on Red Blood Cell Count in 5 Dogs

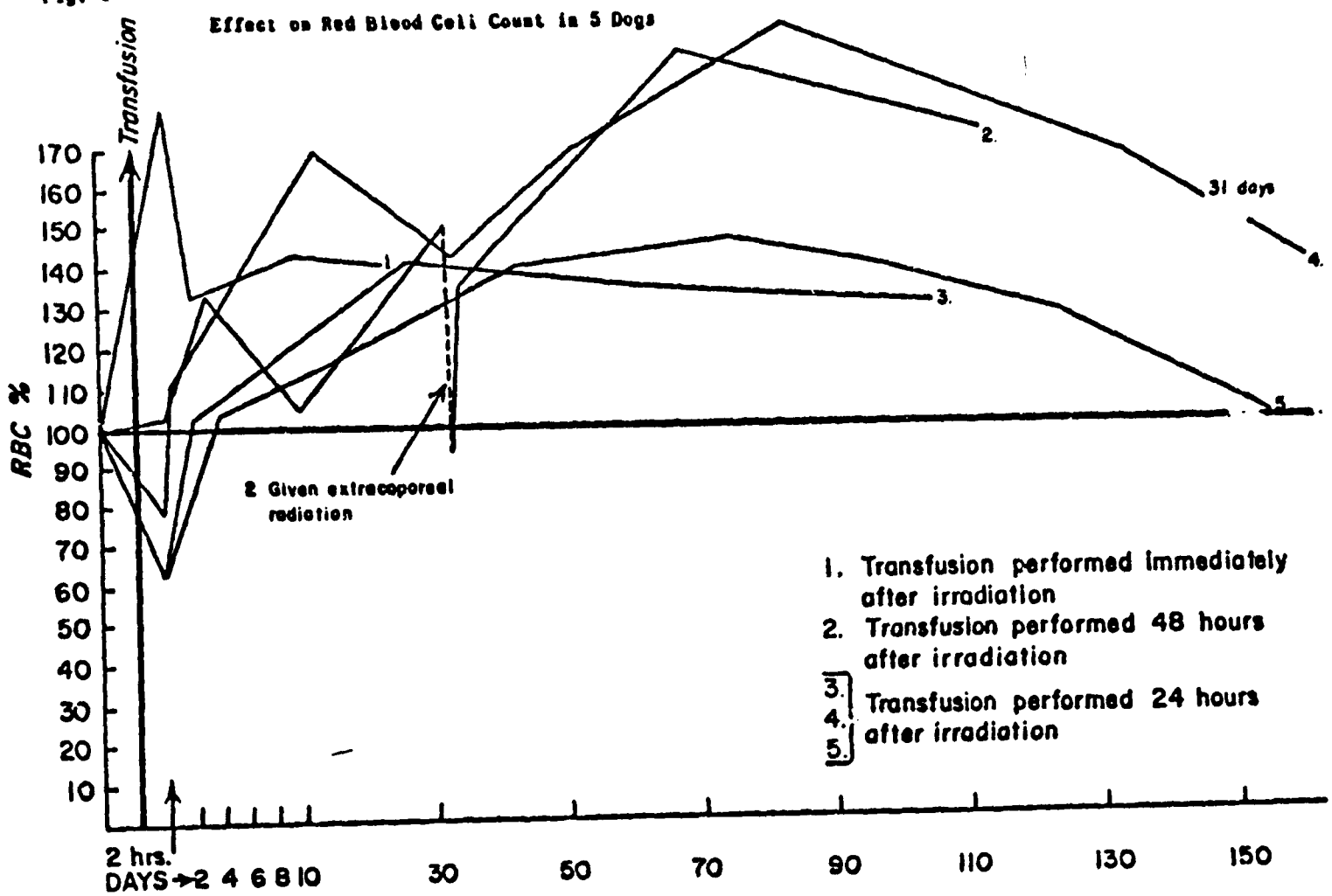


Fig. 13 TRANSFUSION OF EXTRACORPOREALLY IRRADIATED PLASMA

Effect on Hemoglobin in 5 Dogs

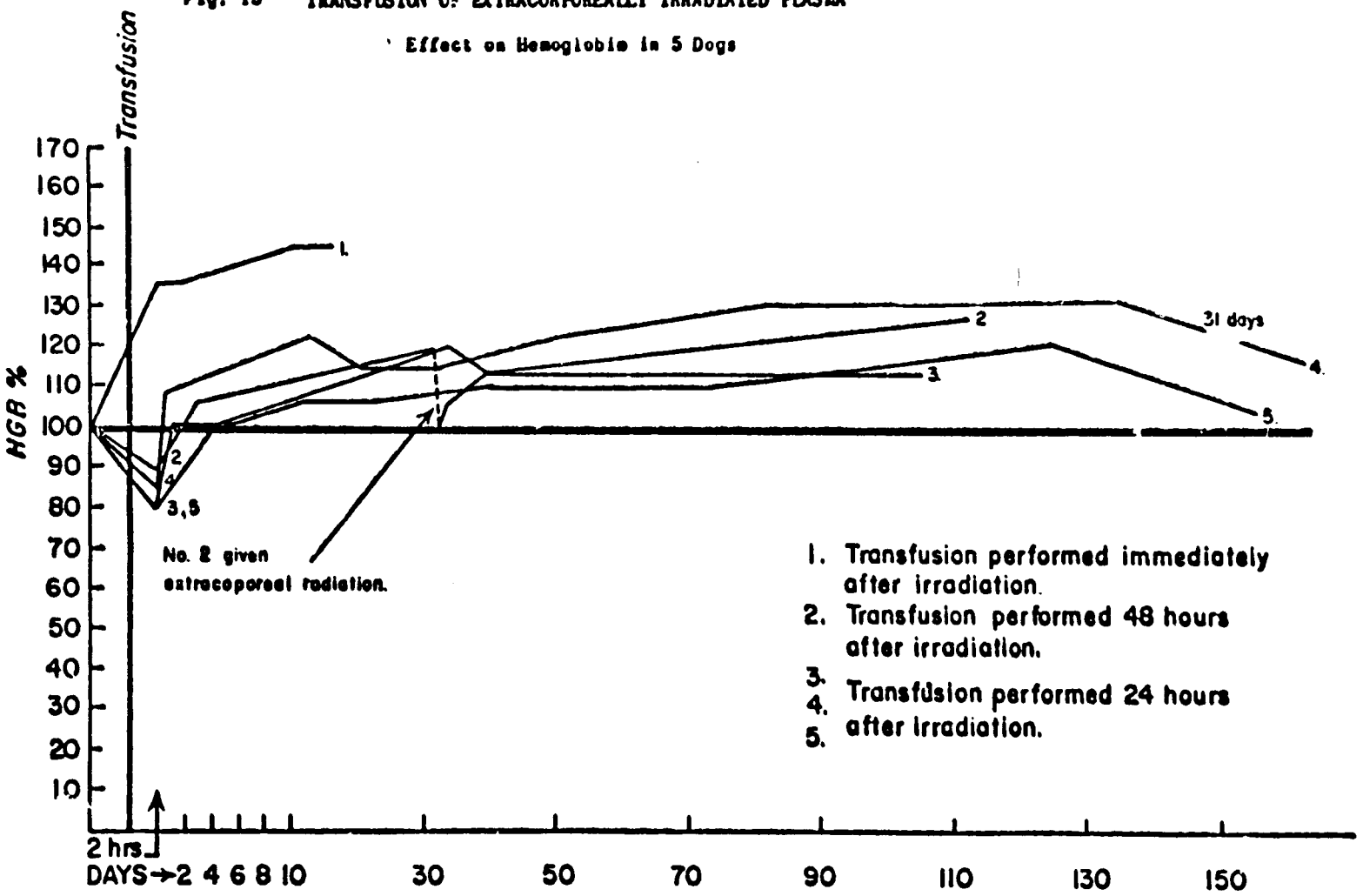


Fig. 14

TRANSFUSION WITH IRRADIATED PLASMA

Effect on White Blood Cell Count in 3 Normal Dogs

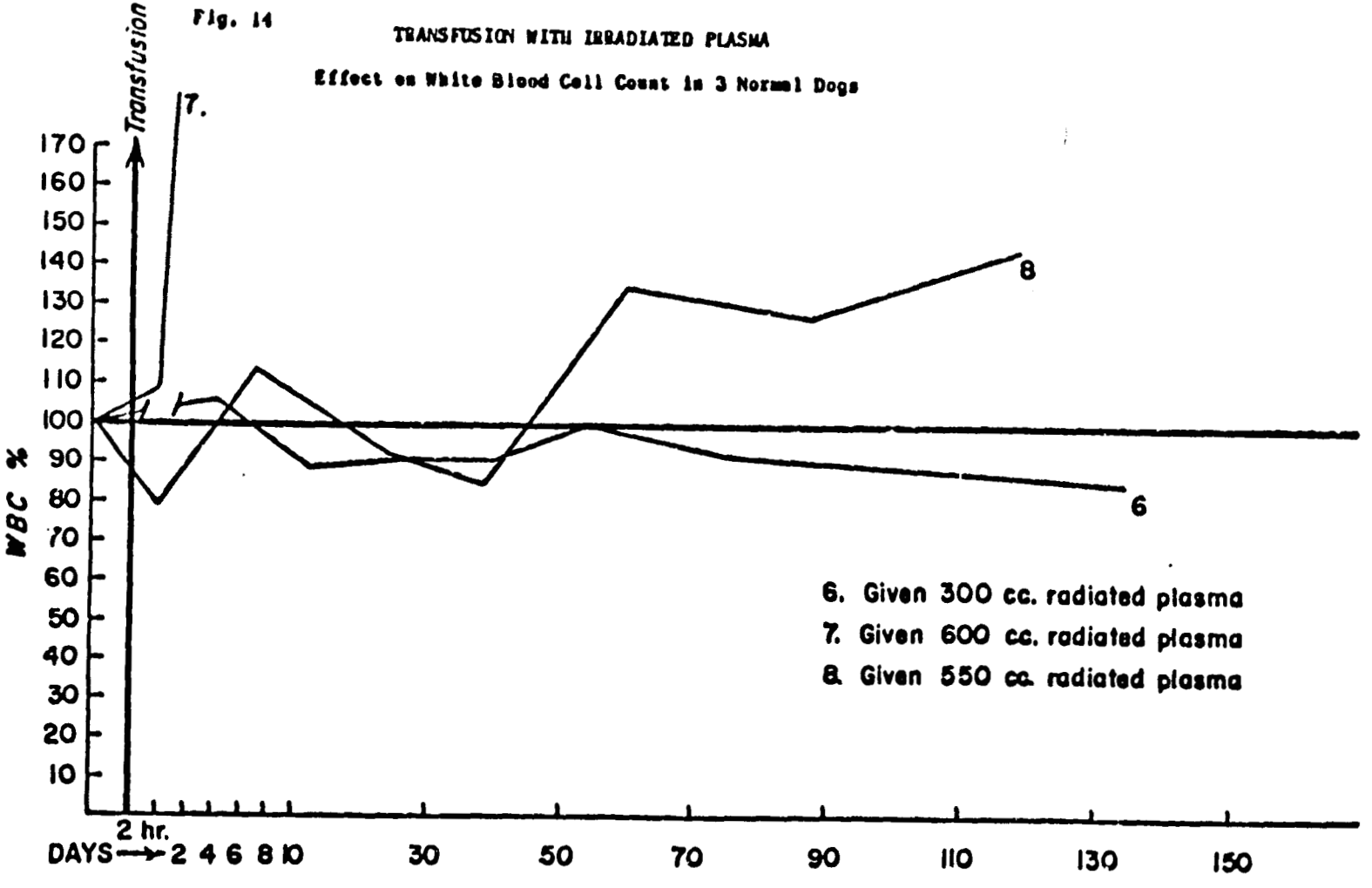


Fig. 15

TRANSFUSION OF IRRADIATED PLASMA

Effect on Red Blood Cell Count in 3 Normal Dogs

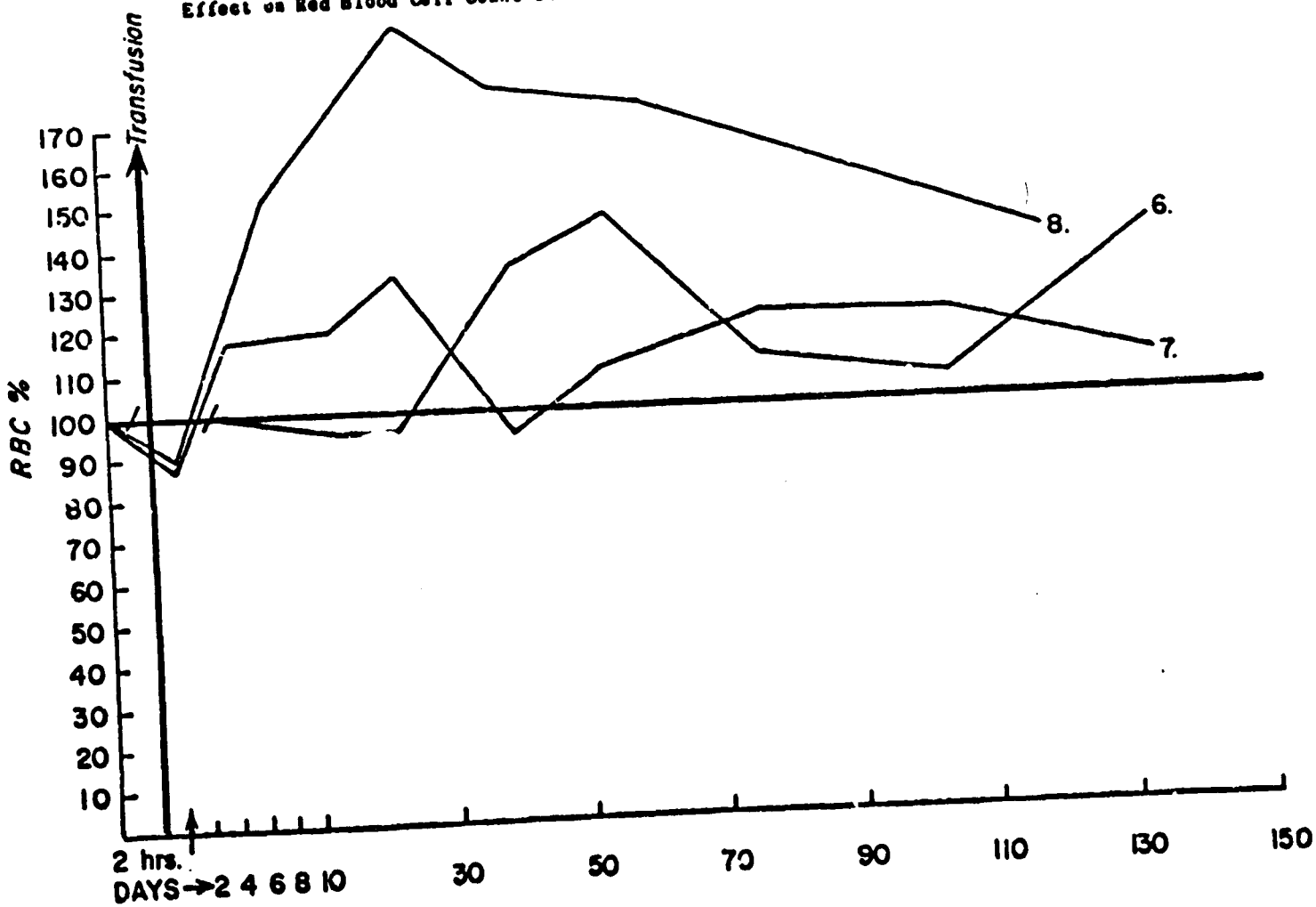


Fig. 16 TRANSFUSION OF IRRADIATED PLASMA

Effect on Hemoglobin in 3 Normal Dogs

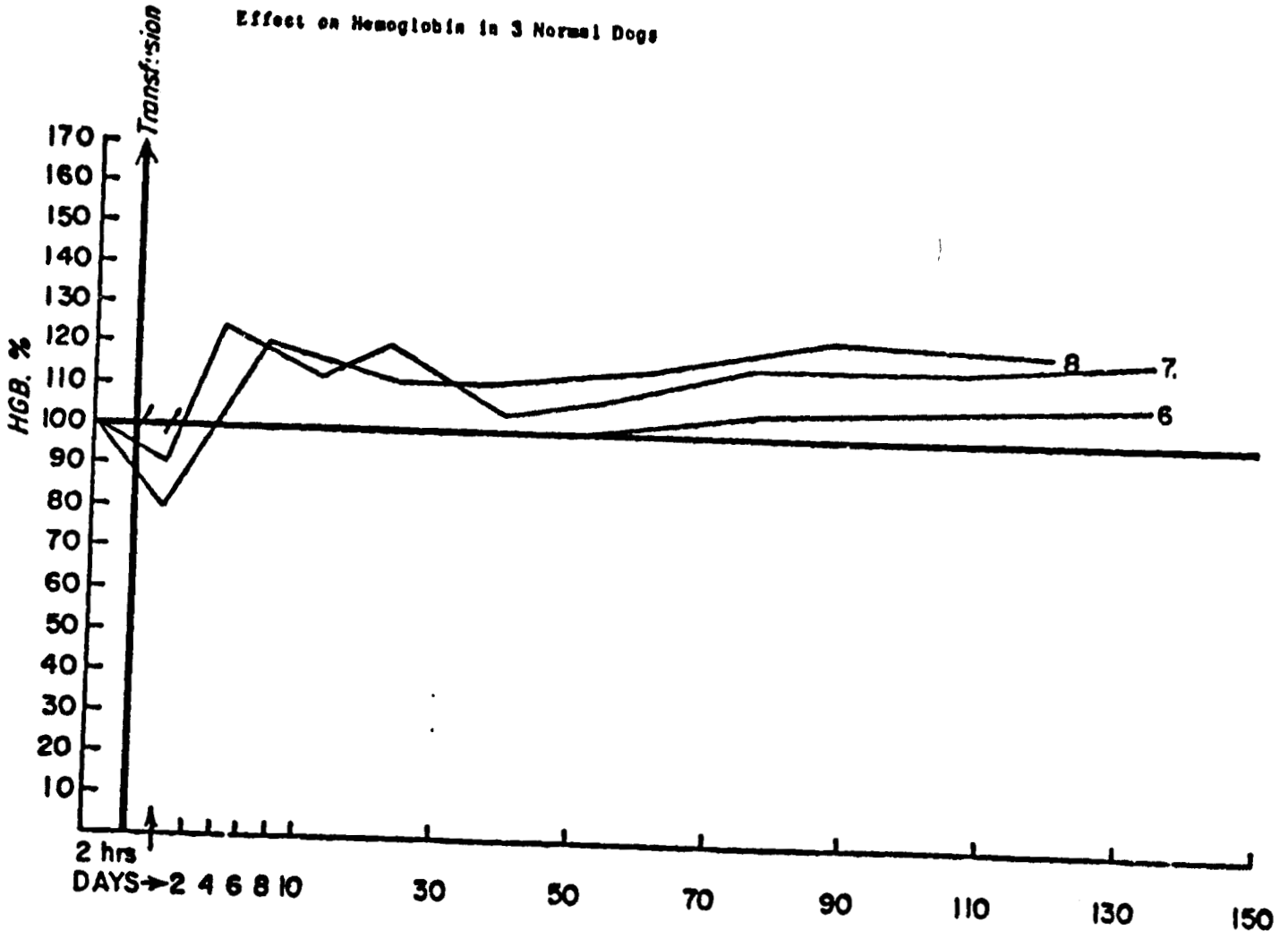


Fig. 17

AUTO-TRANSFUSION OF IRRADIATED WHOLE BLOOD

Effect on White Blood Cell Count

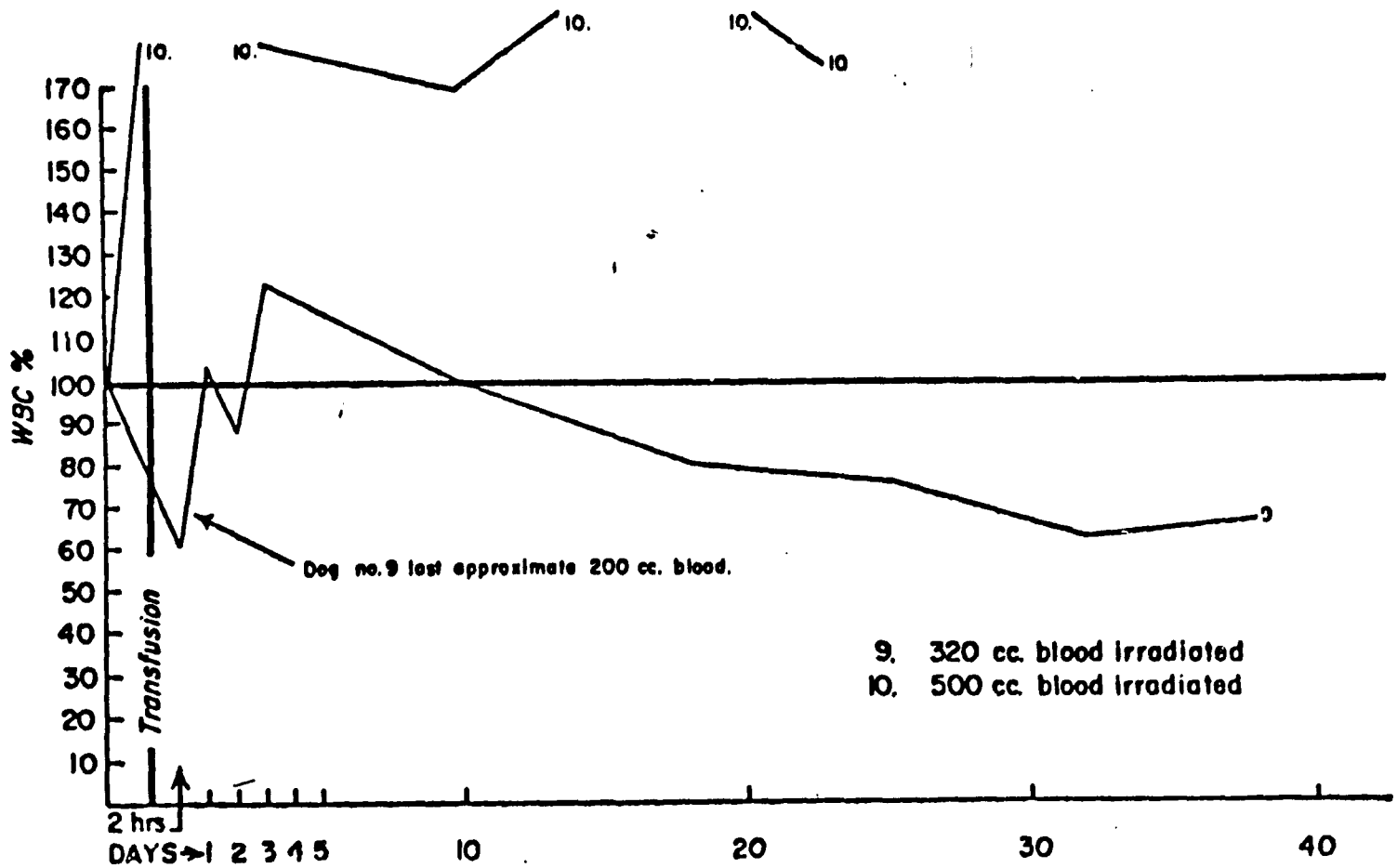


Fig. 18 AUTO-TRANSFUSION OF IRRADIATED WHOLE BLOOD

Effect on Red Blood Cell Count

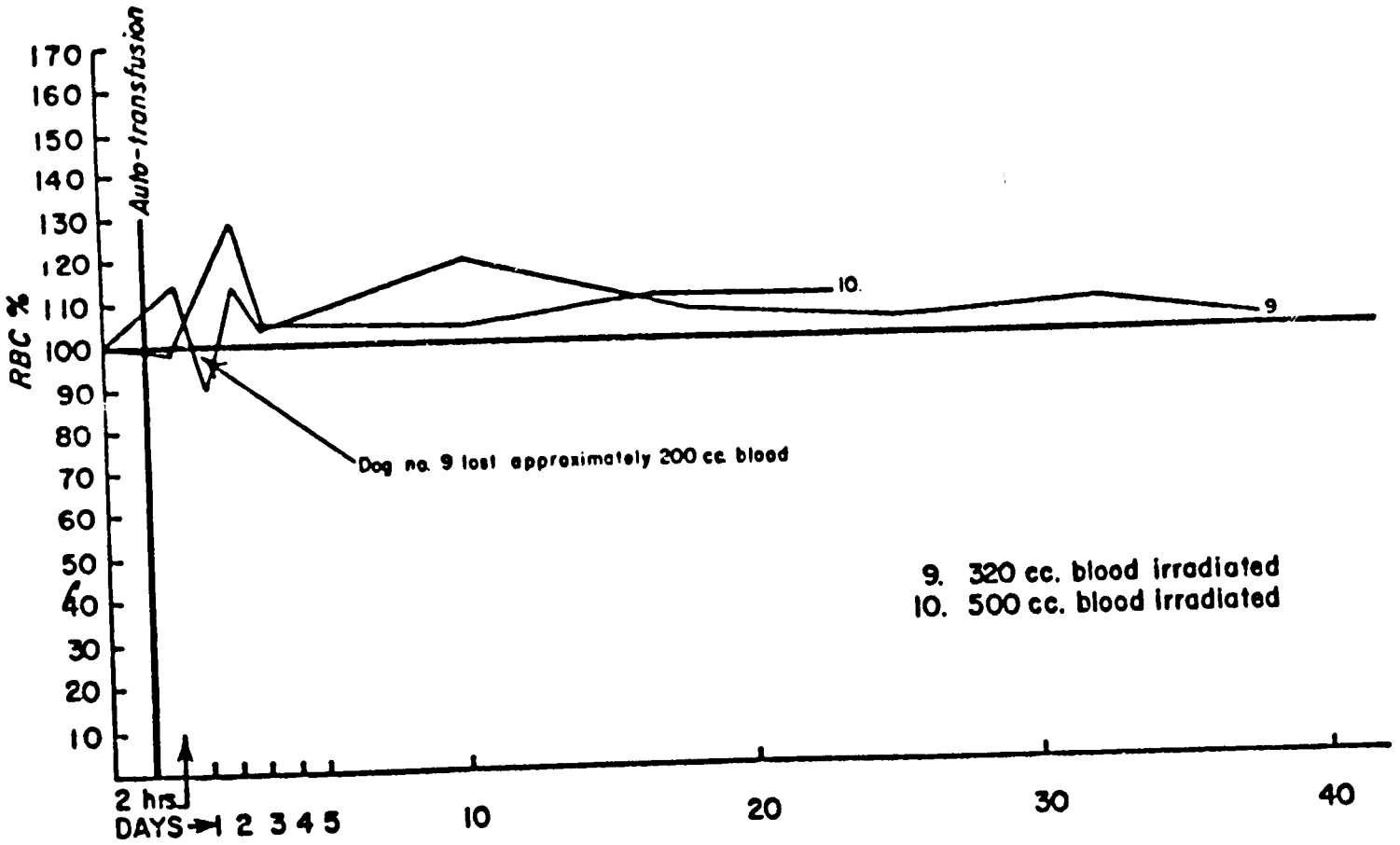


Fig. 19 AUTO-TRANSFUSION OF IRRADIATED WHOLE BLOOD

Effect on Hemoglobin

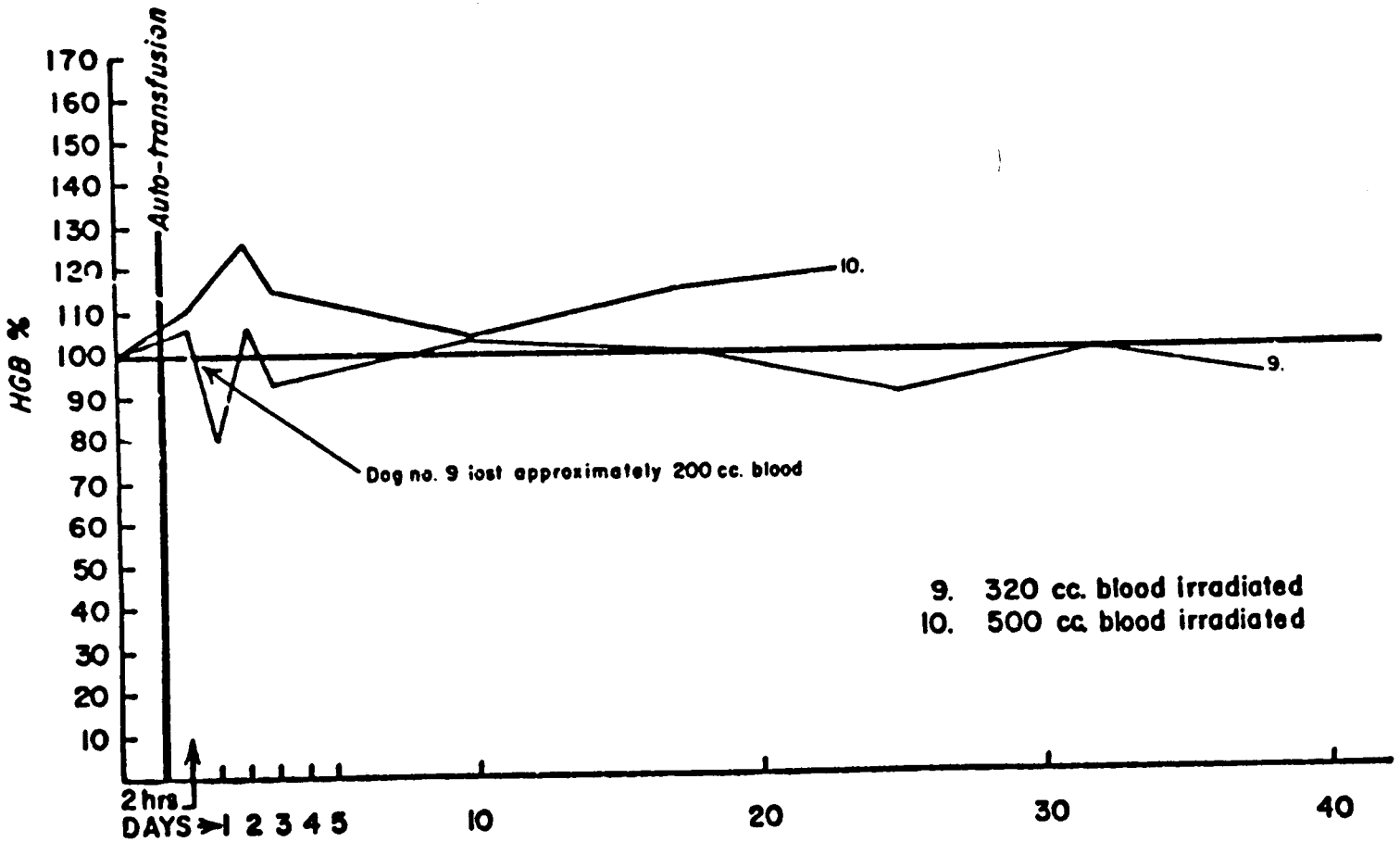


Fig. 20 Hematopoietic Response Following
TOTAL BODY RADIATION and
AUTOTRANSFUSION OF IRRADIATED BLOOD

Patient B. B.
Diag. Ca. of Stomach with ascites
Rx - 100r T.B.R.

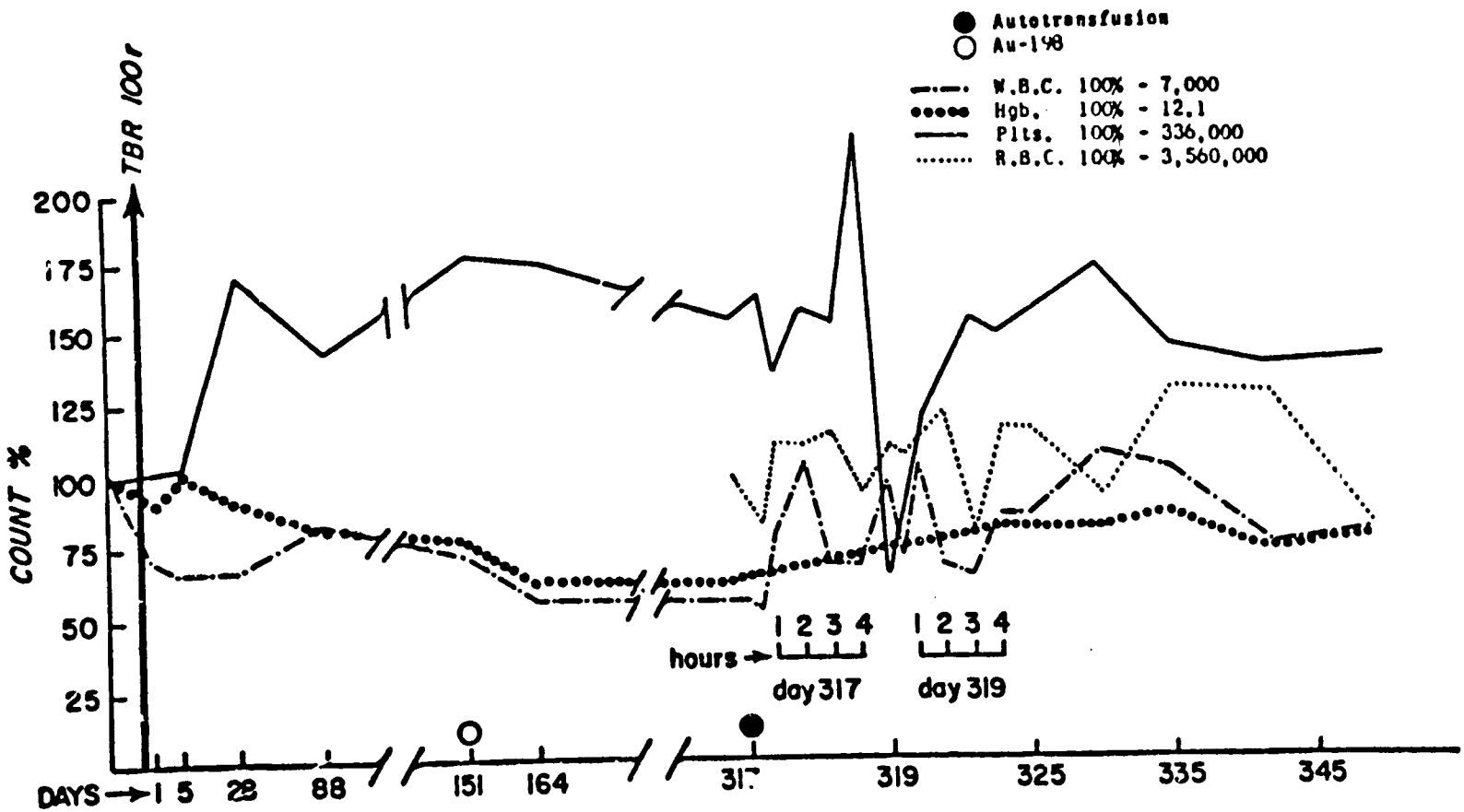


Fig. 21 LETHAL WHOLE BODY RADIATION IN DOGS

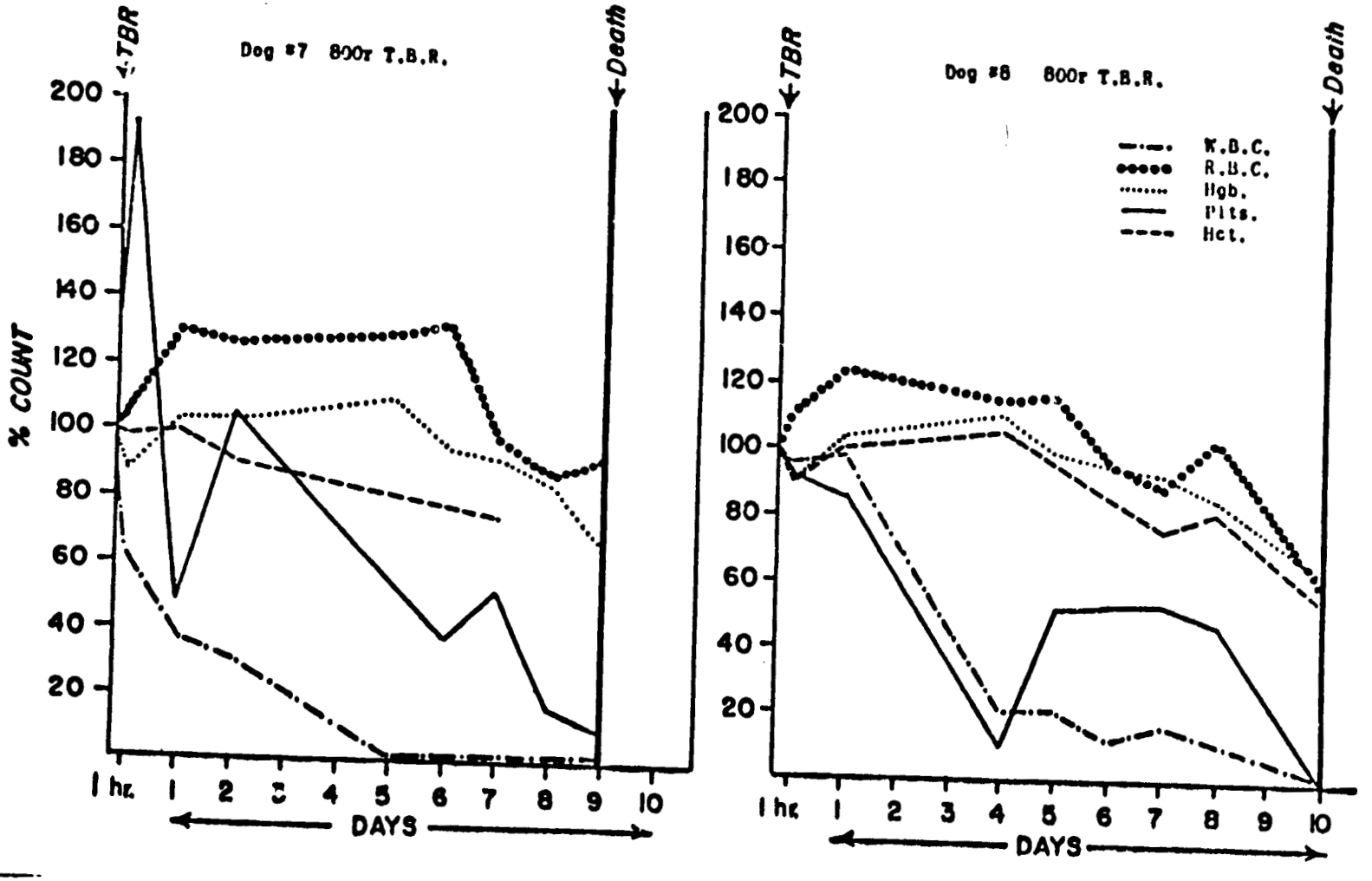


Fig. 22 Response of White Blood Cell Count

TOTAL BODY RADIATION (FRACTIONATED)
241r / 195 days

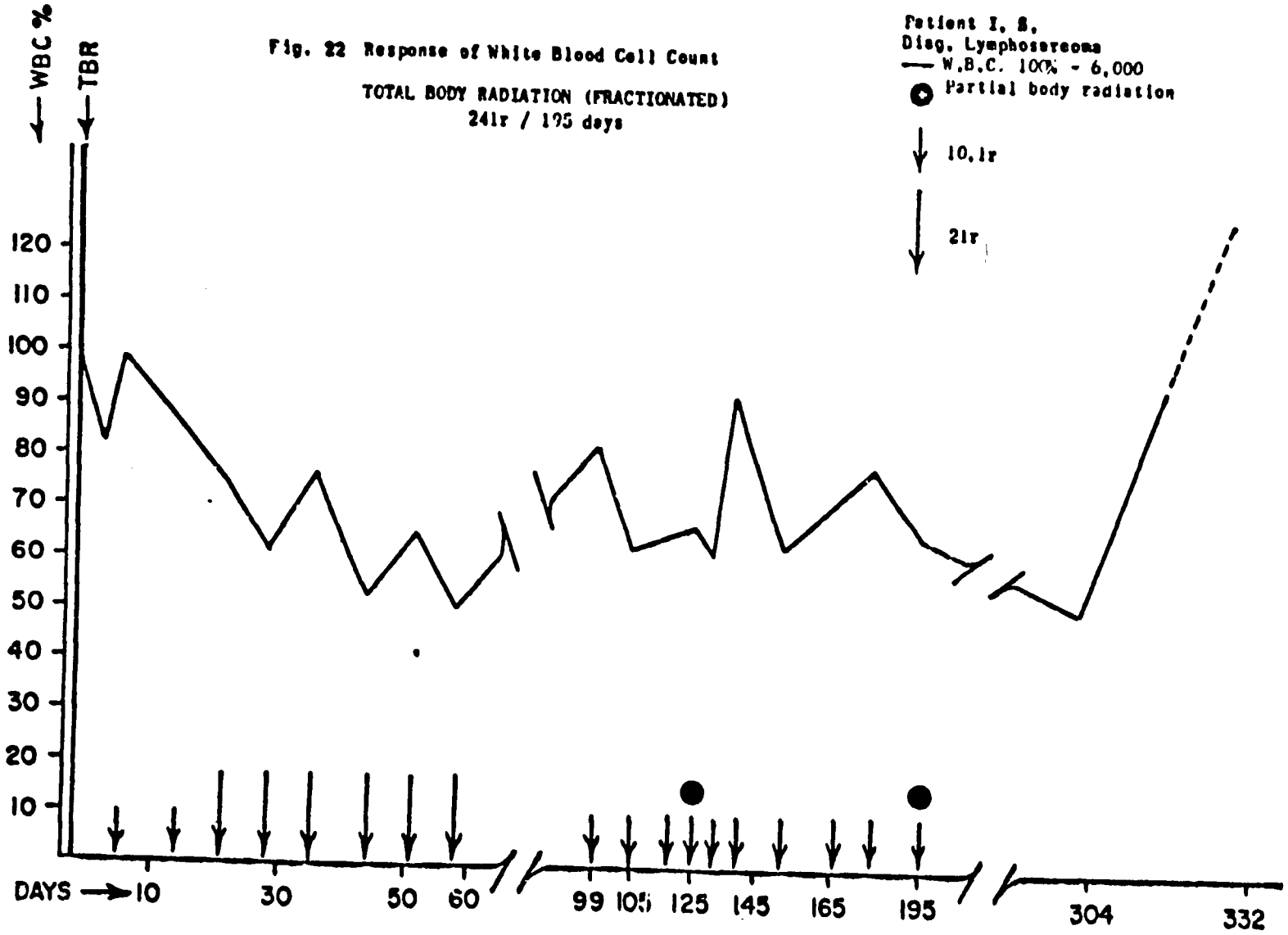
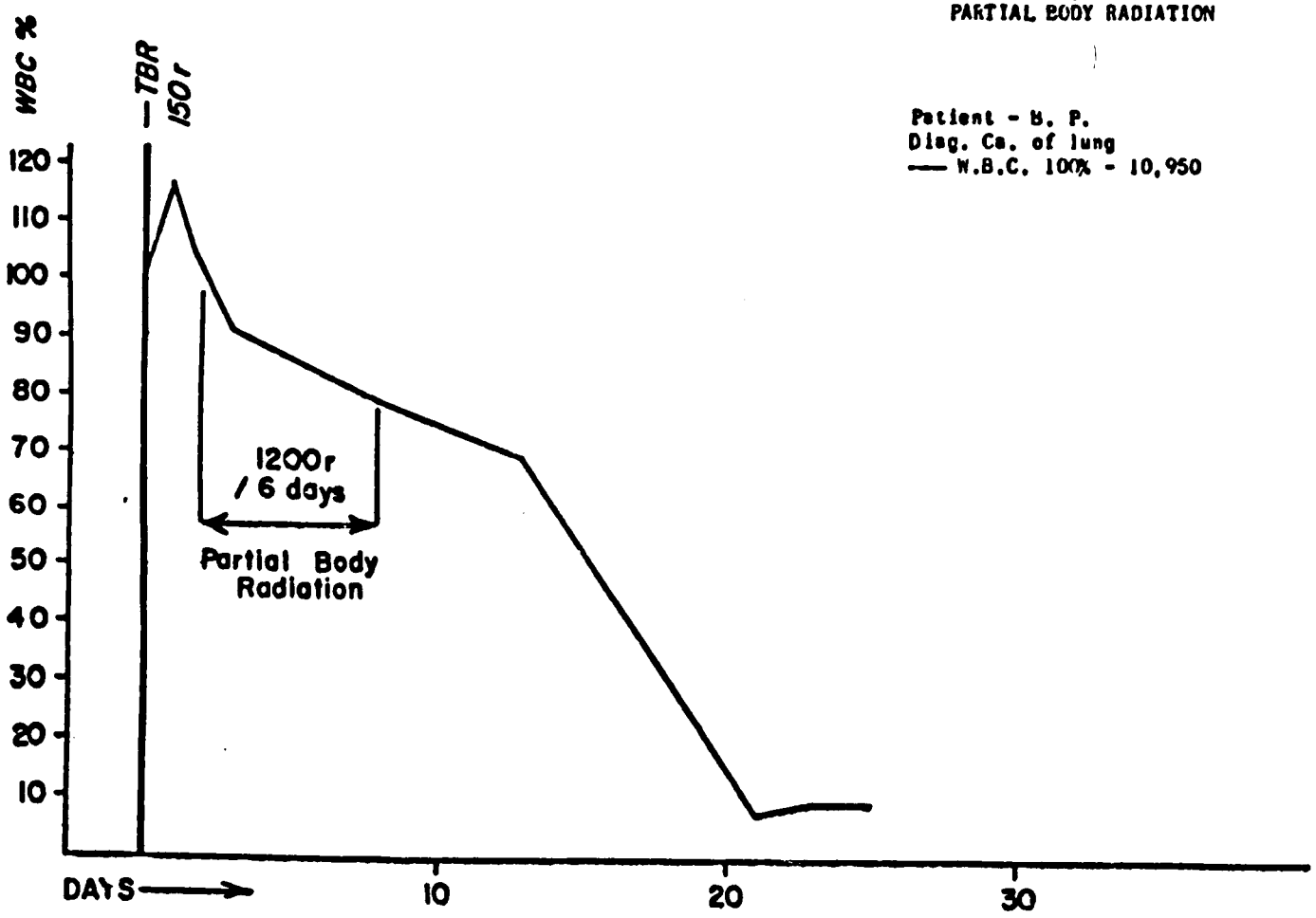


Fig. 23 Response of White Blood Cell Count

TOTAL BODY RADIATION 150r
plus
PARTIAL BODY RADIATION

Patient - B. P.
Diag. Ca. of lung
—— W.B.C. 100% - 10,950