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. 12 pages, 10 illustrations. Dec. 1, 1958 - August 31, 1959

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

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

7. Abstract: This report deals with the following aspects of the investigation.

Response of hematopoietic system following fractionated doses of total body radiation is reported in two patients.

Radiation effect on absorptive function of intestinal mucosa has been studied by measuring absorption of radioiodine labeled serum albumin before and after limited field or total body radiation.

The clinical and hematopoietic response following total body radiation with shielding of critical areas has been studied in a pilot experiment using laboratory animals. The physical condition of the irradiated animals, state of nutrition, and latent infection must be taken into account by carefully preparing animals to minimize the influence of these factors.

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Diagnosis: Ewing's sarcoma of thoracic vertebra with disseminated metastases.

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Extensive pulmonary metastases developed to the point of pulmonary embarrassment, (Fig. 1 A).

August 8 - 28, 1958 TOTAL BODY RADIATION 300r/20 days

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Since intestinal mucosa is considered one of the most radiosensitive tissues, it seemed possible that there might be a measurable effect of radiation on absorption from the intestine. Observations have been made on the absorption of radioiodine labeled serum albumin before and after whole body or limited field radiation therapy.

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1. In several cases the per cent absorption of RISA after radiation therapy appears to be higher than the values for the control series.

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Four normal dogs of comparable physical characteristics, with an average weight of 13.5 kilograms were used in this experiment. Total body radiation was given with the 2 m v Van de Graaff generator (half value layer 9 mm. lead), two animals receiving 200r and two receiving 400r. One dog receiving 200r and one receiving 400r were irradiated without shielding as controls. The other two animals had partial shielding as illustrated in figure 4. The lead shields were 9 mm. in thickness, thus reducing radiation to one half in the protected areas. Two shields 7 x 8 cm. covered the outer aspects of clavicle and upper ends of humerus on each side, a single 5 x 12 cm. shield covered the entire pelvis and upper ends of femora. Unprotected areas of red bone marrow included lower ends of femora and humeri, all of fibulae, tibiae, ulnae and radii, and portions of spine and ribs; these areas received full dosage of radiation.

Figure 5 A shows the white blood cell count and platelet response in the two control animals (No. 88 and No. 91) following total body radiation 200r and 400r respectively without shielding. No. 91 died 13 days after receiving 400r. No. 88, receiving 200r, showed maximum depression on the 18th day with return to normal on the 28th day.

Figure 5 B shows the response of white blood cell count and platelets in two animals receiving total body radiation, 200r and 400r respectively, with shielding as shown in figure 4. No. 90, receiving 400r showed maximum depression (25% of normal) on the 4th day while No. 89, receiving 200r, showed depression to 68% of normal on the 4th day; beginning recovery was noted between the third and fourth week.

Comparison of the two figures shows initial elevation of platelets followed by depression in all four animals. The elevation of platelets was higher and depression of both platelets and white blood cell count was less severe in the shielded animals. Comparison of No. 88 (200r unshielded) and No. 89 (200r with shields) shows a difference in the time and degree of depression. In the unshielded animal, the white blood cell count reached the lowest point (38% of normal on the 18th day; in the unshielded dog. the white blood cell count reached the lowest point (60% of normal) on the 31st day.

Figure 6 A shows the red blood cell count and hemoglobin response in the control animals and figure 6 B showed the response in the animals with partial body shielding. Comparison of response of the two animals receiving 400r, one unshielded and one with partial shielding of bone marrow, shows a striking difference. Autopsy and bone marrow studies were done on the unshielded animal; pathology report: complete aplasia of bone marrow. The shielded animal recovered promptly, indicating that the sparing effect of partial shielding of bone marrow may insure recovery when doses are of this order. All surviving animals recovered promptly and have remained healthy; at no time was there evidence of nausea, vomiting or diminished appetite or activity. The protective effect of shielding could be of obvious importance but this might be masked or exaggerated when the lethal dose of radiation may be influenced by general physical condition, nutritional status and uncertain breed.

Experience of many individuals with irradiation of dogs has resulted in considerable variation in opinion as to the $L.D._{50}$ and $L.D._{100}$. Among the reasons for this are the relatively small number of animals studied, variations in quality of radiation, geometry of irradiation, and methods of measuring and recording exposure dose. The factors of nutrition, general physical condition and breed may further influence the tolerance to radiation. To reduce some of these variables, it is necessary to undertake radiation of control animals, giving particular attention to their nutrition and general health.

Six dogs were selected and prepared for radiation over a period of about 4 weeks. All received inoculations for distemper and rabies and all received an adequate and balanced diet. All animals were kept in quarantine for 9 days and then were placed in semi-quarantine (separate cages) where the remained throguhout the period of observation. Preceding irradiation, blood counts were taken daily for one week and every other day thereafter (1 to 2 weeks) until the blood count stabilized and a normal base line was obtained. Three of the animals received 400r and three received 500r total body radiation with 2 m v. All animals survived and all showed a uniform depression of white blood cell and platelet count with recovery beginning about 3 weeks after irradiation and returning to normal at about 7 weeks.

Figure 7 shows the white blood cell count and platelets in 3 animals following 400r total body radiation; figure 8 shows the white blood cell and platelets in 3 animals following 500r total body radiation. In both groups the platelet count dropped sharply (5 to 20% of normal) by the 11th day and remained at this level until recovery began about three weeks after exposure. In the three dogs receiving 400r, white blood cell depression ranged from 8 to 32 per cent of normal; in the 3 recei..g 500r, depression ranged from 20 to 28 per cent of normal. In spite of severe depression of both white blood cell count and platelets, there was no evidence of bleeding or infection. No supportive therapy of any kind was offered. Recovery began about the 3rd week and by the 7th week complete recovery was noted in one of the 400r group and in two of the 500r group.

Figures 9 and 10 show the response of hemoglobin, hematocrit and red blood cell count with the expected red cell survival rate. None of these fell below 60 per cent of normal. In both groups the fall in red cell count corresponded roughly with the expected 1 per cent per day decrease, based on red cell life span, until recovery began at about the 3rd week.

This demonstration of the effect of nutrition and general health upon tolerance to radiation is no surprise but the importance may have been under estimated. For critical observations it might be necessary to use pure bred dogs.

The direction of further investigation is to study factors which influence tolerance and recovery such as partial body shielding and bone marrow transplants. Preliminary work must be done on large animals such as dogs or small primates. In determining the factors that influence tolerance and recovery, a firm estimate of lethal dose of radiation is essential and this will require that the factors of nutrition, infection, general health and breed must be considered.

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Patient	Diagnosis	Radiotherapy			% RISA Absorption					% RISA Absorption					Remarks
		Date	Daily Dose	Total Dose	Date	0-2 hrs	2-4 hrs	4-6 hrs	24 hrs	Date	0-2 hrs	2-4 hrs	4-6 hrs	24 hrs	
J.B.	Chronic lymphatic leukemia	2-24-58 7-17-58	50 (TBR)	350 (TBR)	3-17-58	10.2	9.0	7.3	3.8	4-30-58	10.7 15.8 16.8 15.2	13.9			
A.W.	Hepatoma	5-13-58 5-14-58	200	400	5-14-58	1.4	2.3	3.0							Deceased
T.T.	Carcinoma of bladder	6-19-58 7-9-58	300	4200	6-19-58	-	10.0	11.0							Did not keep app
E.B.	Carcinoma of lung	6-26-58 7-10-58	200	1600	6-25-58	8.0	6.0	4.7		7-10-58	9.0	6.8	6.6		
B.F.	Carcinoma of vaginal cuff	6-26-58 7-17-58	300	4500	6-25-58	11.0	9.0	7.3		7-31-58	26.5	46.1 45.0			
G.C.	Carcinoma of lung	6-26-58 7-30-58	300	6000	6-25-58	9.0	6.6	5.7		8-11-58	13.9	12.0	11.0		
H.A.	Retro-bulbar tumor	7-29-58 8-8-58	250	2300	7-23-58	4.3	4.1			8-18-58	10.2	8.8			
B.R.	Carcinoma of cervix	8-15-58 9-7-58	200	3000	7-23-58	5.8	8.0								Did not keep appt
H.S.	Carcinoma of cervix	8-18-58 9-10-58	200	3000	7-24-58	5.6	5.1			10-3-58	10.9	10.4			

RISA Absorption From Bowel Before And After Radiation

8-4-58

Fig. 1 A. Chest film showing pulmonary metastases before treatment.

9-29-58

Fig. 1 B. Chest film showing response of pulmonary metastases to total body radiation.

Fig. 2. Case 1 K.R.

TOTAL BODY RADIATION

Response of White Blood Cell Count and Platelets Following 50r x 6 in 20 days (2 m v)

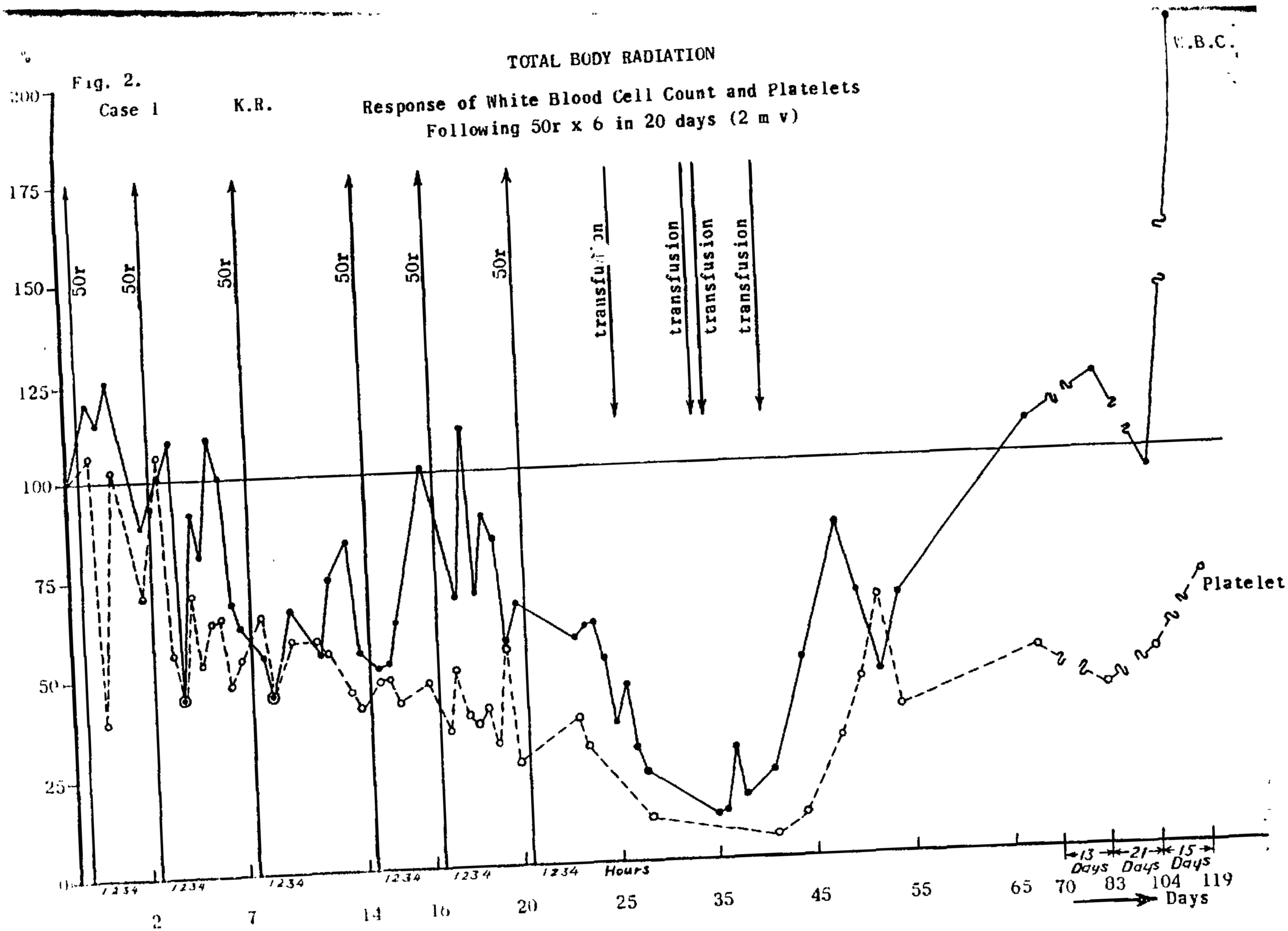

Fig. 3

Case 2. A.S. LARGE FIELD AND TOTAL BODY RADIATION
Response of Peripheral Blood Count

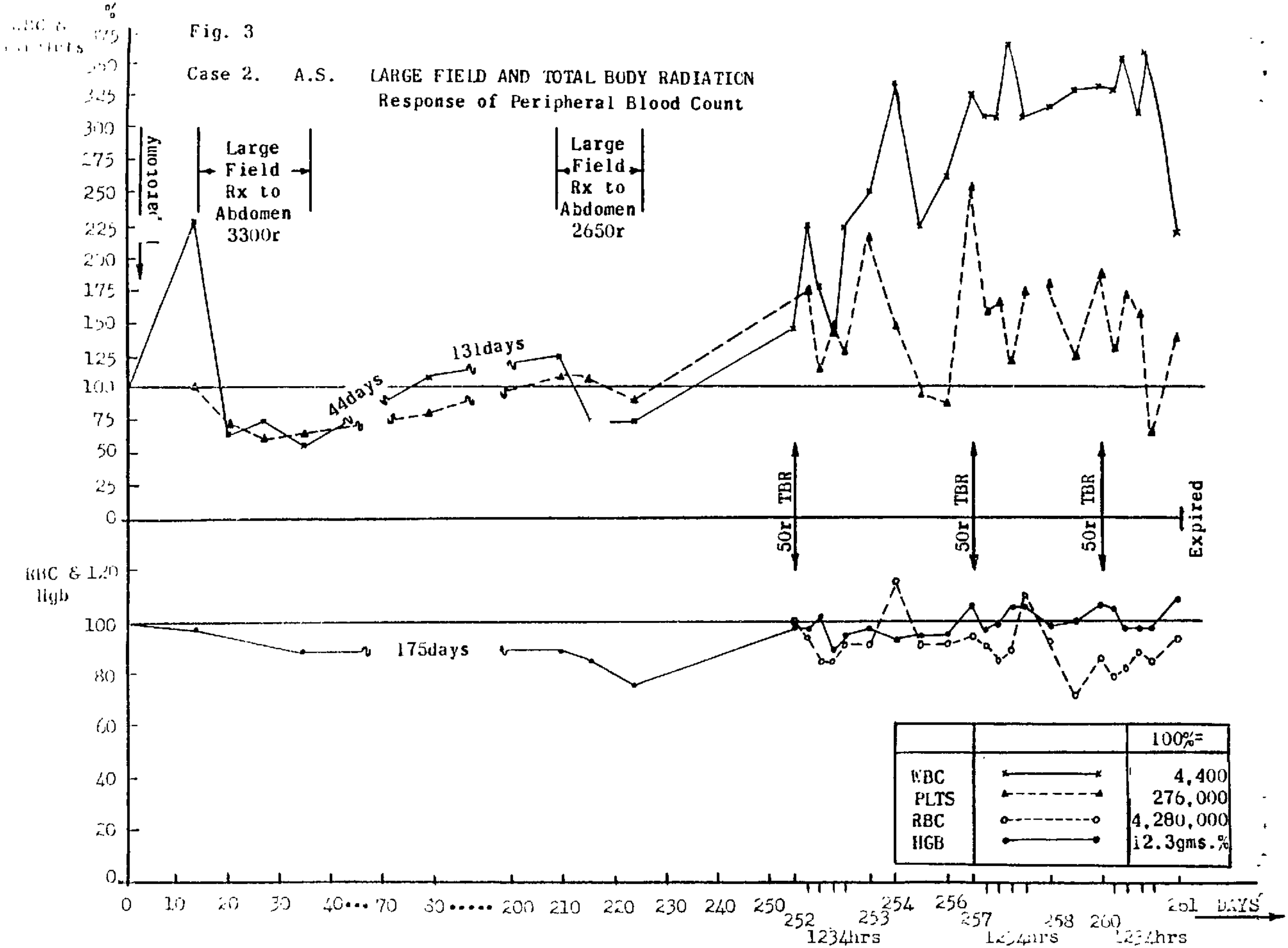

Fig. 4. Distribution of Shields (9 mm. lead) for Protection of Bone Marrow During Total Body Radiation

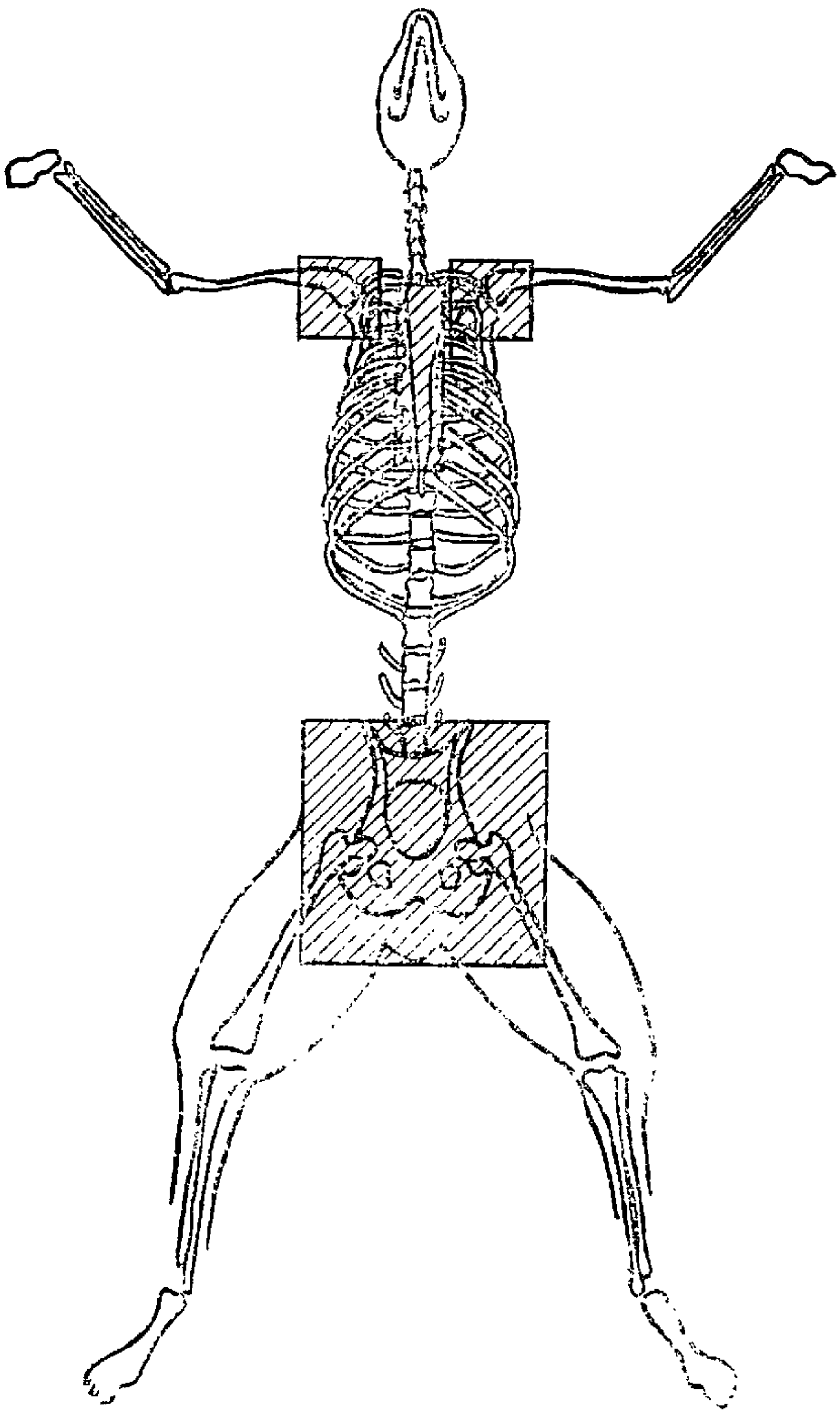

Fig. 5 A.

Response of White Blood Cell Count and Platelets
Following Unshielded Total Body Radiation

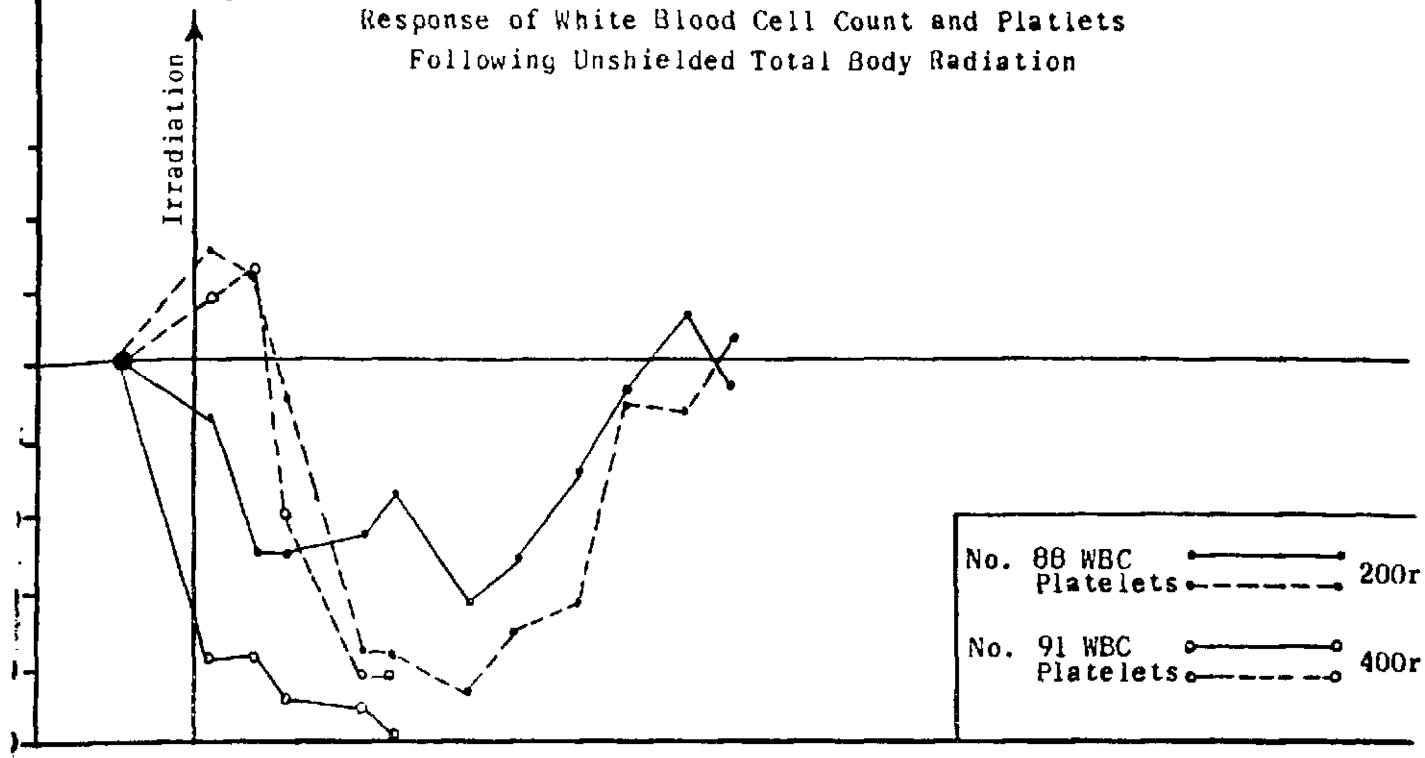

Fig. 5 B.

Response of White Blood Cell Count and Platelets
Following Total Body Radiation With Shields

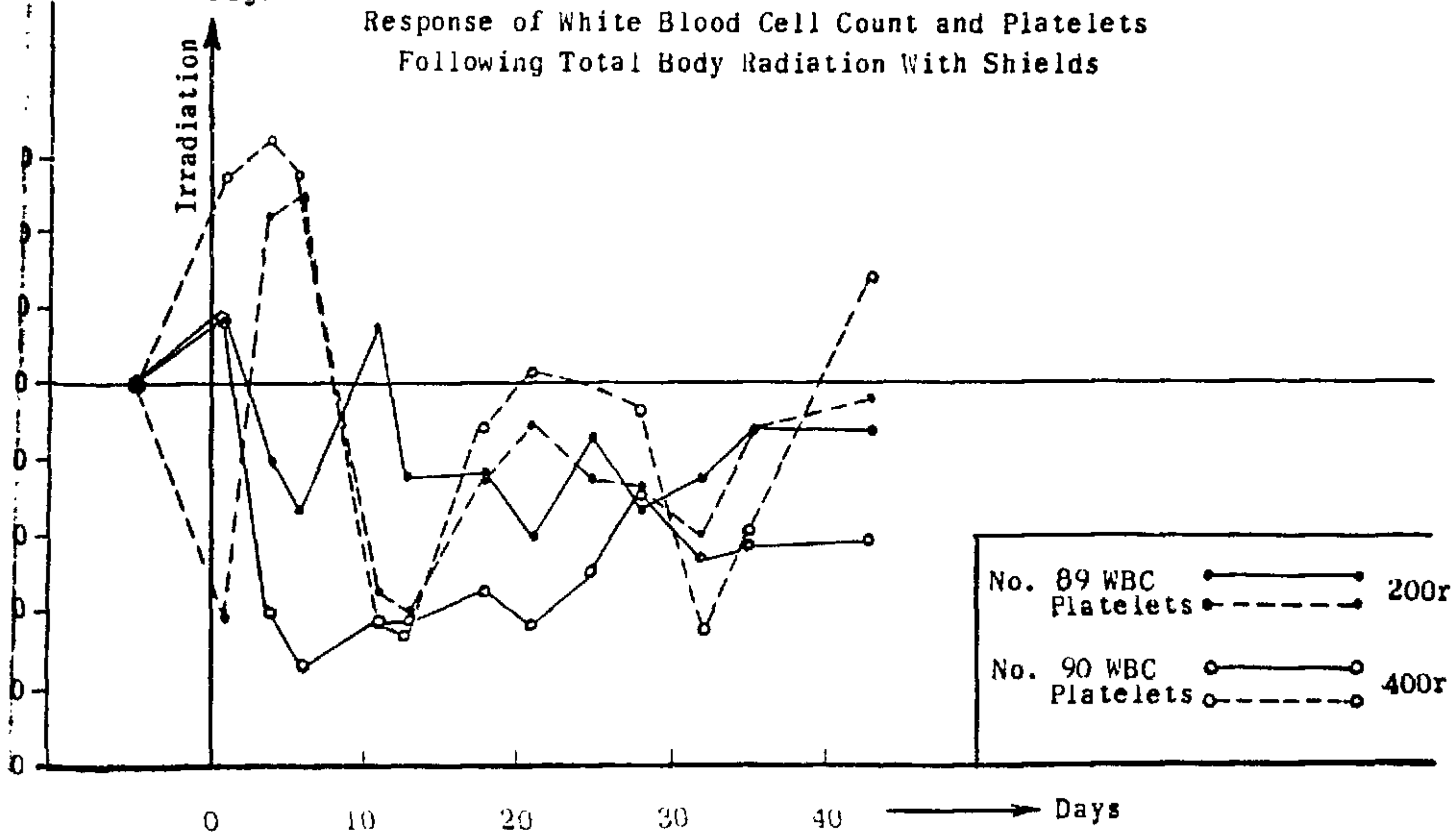

Fig. 6 A. Response of Red Blood Cell Count and Hemoglobin Following Unshielded Total Body Radiation

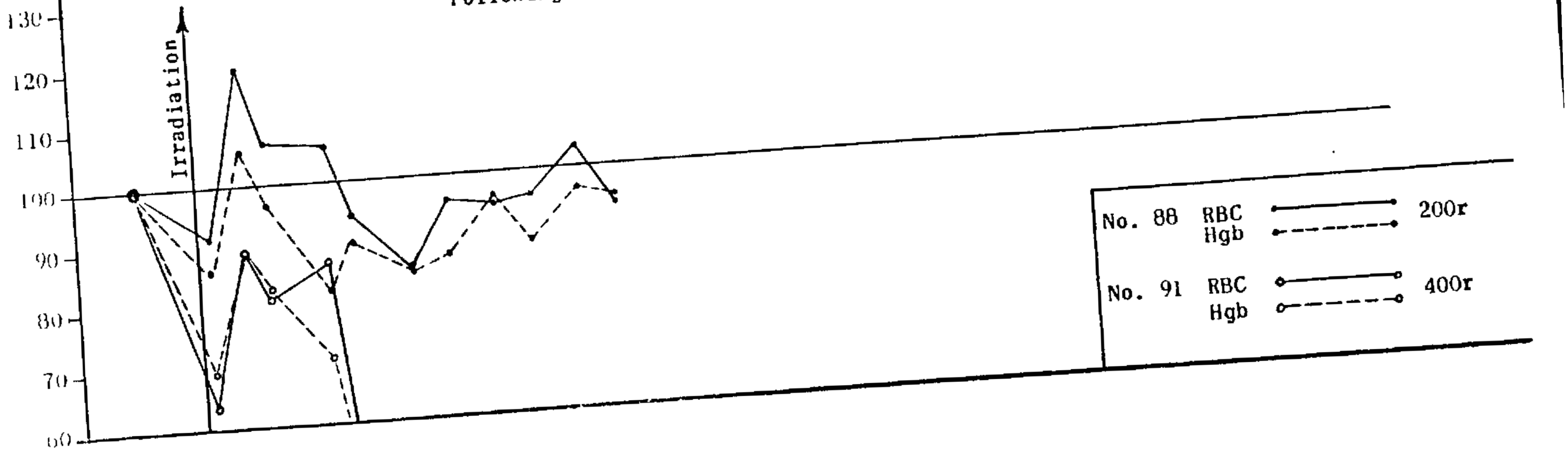

Fig. 6 B. Response of Red Blood Cell Count and Hemoglobin Following Total Body Radiation with Shields

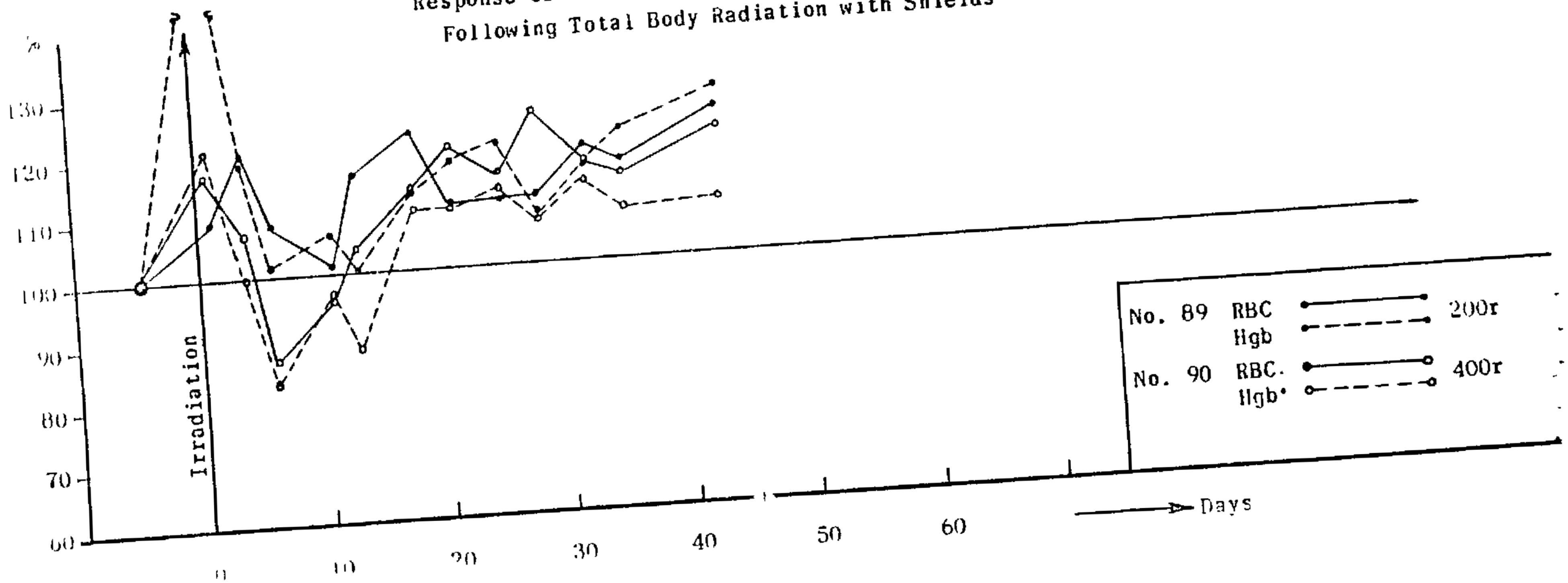

Fig. 7.

TOTAL BODY RADIATION
Response of White Blood Cell Count and Platelets
in 3 Dogs Receiving 400r

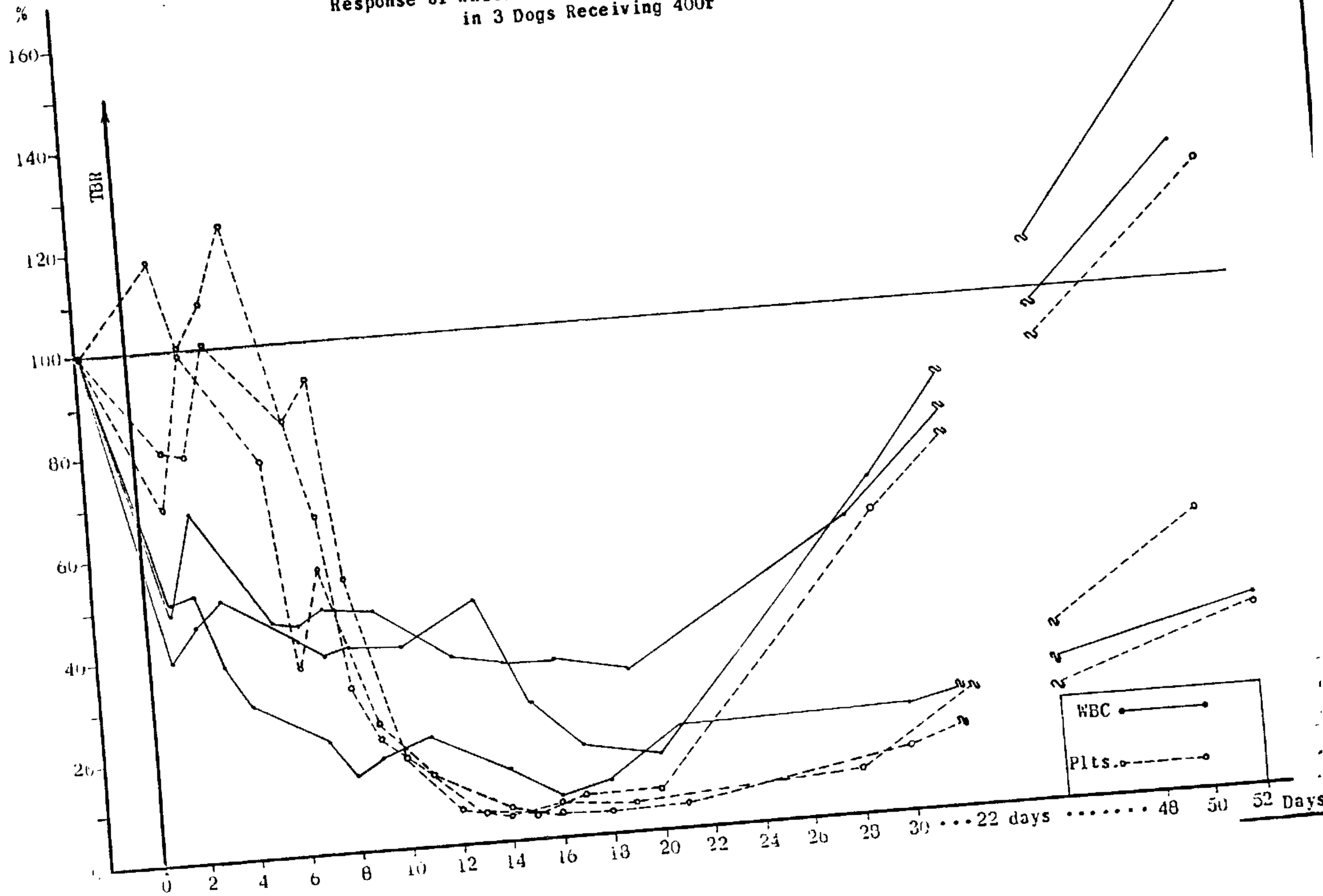

Fig. 8.

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Response of White Blood Cell Count and Platelets in 3 Dogs Receiving 500r

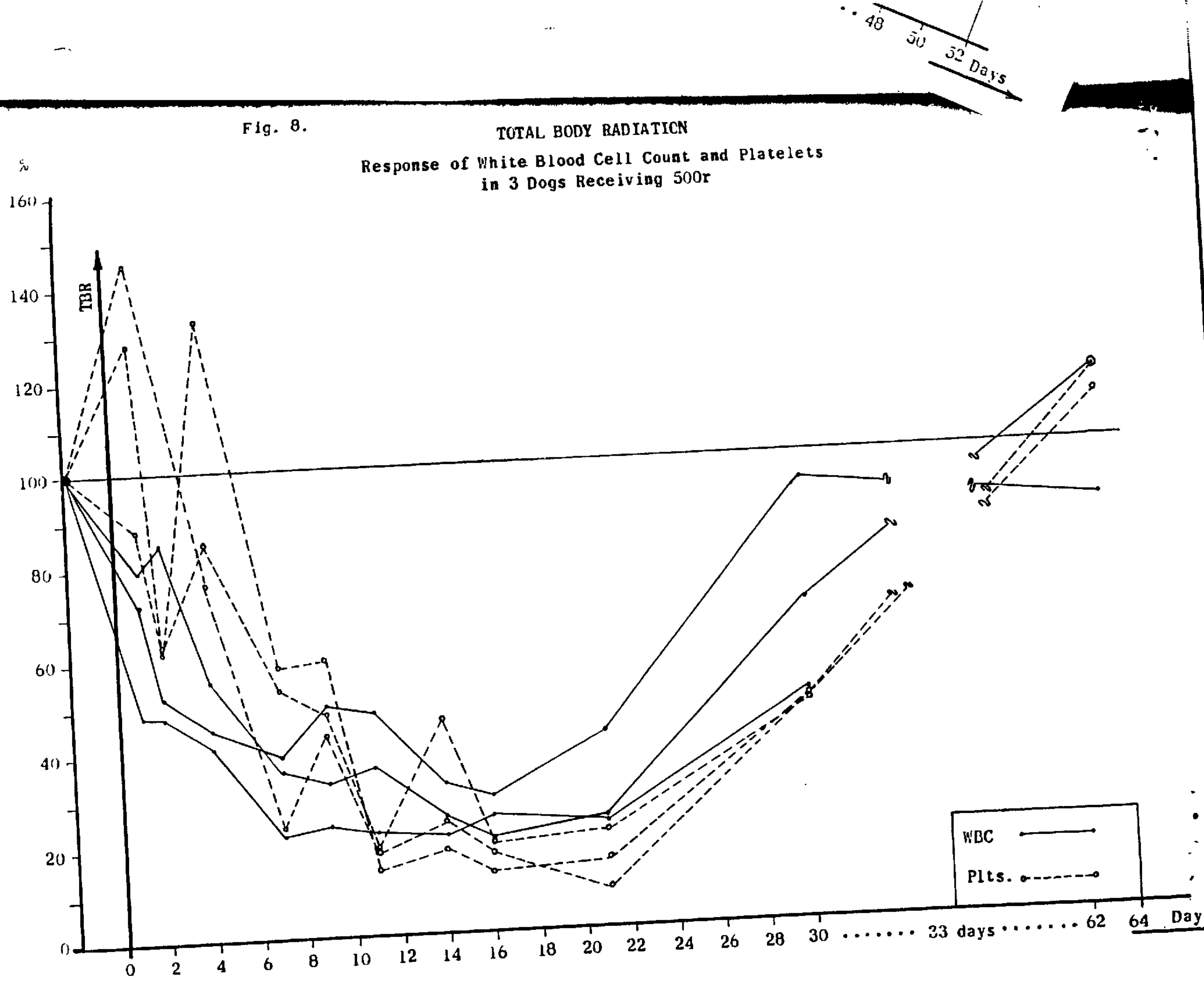

Fig. 9. TOTAL BODY RADIATION

Response of Red Blood Cell Count, Hemoglobin and Hematocrit in 3 Dogs Receiving 400r

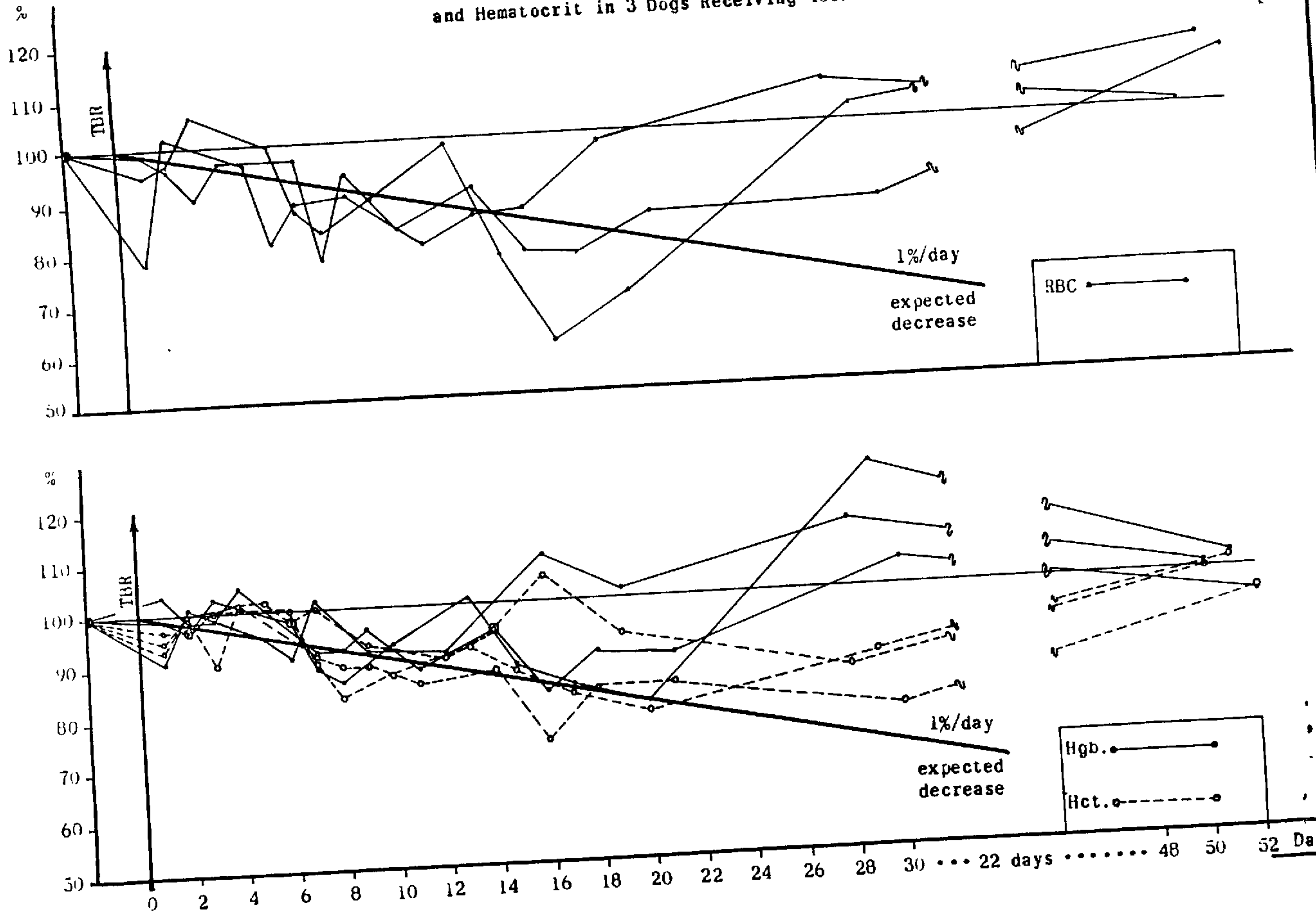

Fig. 10

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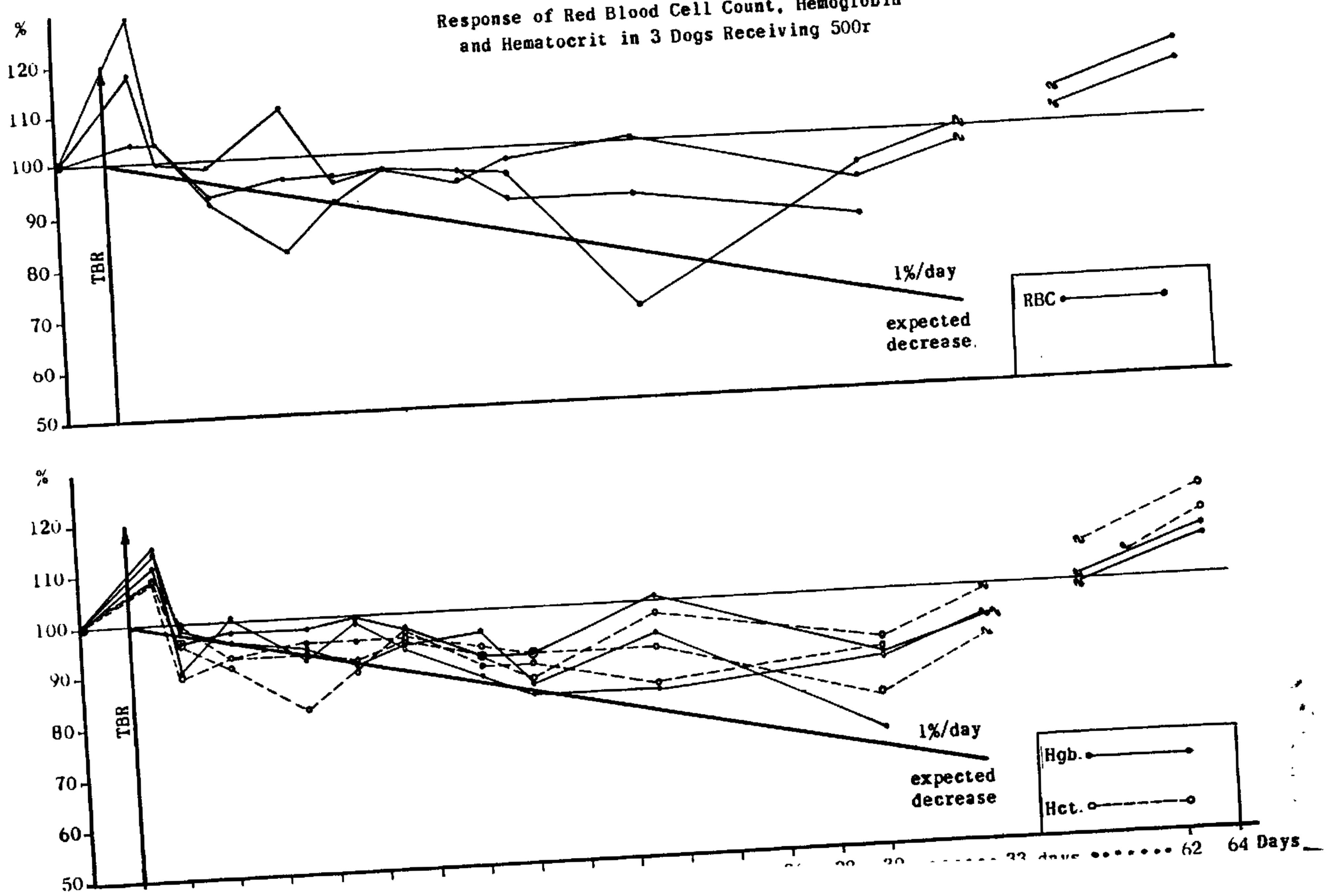

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Initially, consideration was given to how the site and area of partial body shielding in dogs might influence the dose of radiation that can be tolerated. For partial body radiation, unirradiated hematopoietic tissue is believed to sustain the individual in a dosage range far beyond the tolerated dose for total body radiation.

Four normal dogs of comparable physical characteristics, with an average weight of 13.5 kilograms were used in this experiment. Total body radiation was given with the 2 m v Van de Graaff generator (half value layer 9 mm. lead), two animals receiving 200r and two receiving 400r. One dog receiving 200r and one receiving 400r were irradiated without shielding as controls. The other two animals had partial shielding as illustrated in figure 4. The lead shields were 9 mm. in thickness, thus reducing radiation to one half in the protected areas. Two shields 7 x 8 cm. covered the outer aspects of clavicle and upper ends of humerus on each side, a single 5 x 12 cm. shield covered the entire pelvis and upper ends of femora. Unprotected areas of red bone marrow included lower ends of femora and humeri, all of fibulae, tibiae, ulnae and radii, and portions of spine and ribs; these areas received full dosage of radiation.

Figure 5 A shows the white blood cell count and platelet response in the two control animals (No. 88 and No. 91) following total body radiation 200r and 400r respectively without shielding. No. 91 died 13 days after receiving 400r. No. 88, receiving 200r, showed maximum depression on the 18th day with return to normal on the 28th day.

Figure 5 B shows the response of white blood cell count and platelets in two animals receiving total body radiation, 200r and 400r respectively, with shielding as shown in figure 4. No. 90, receiving 400r showed maximum depression (25% of normal) on the 4th day while No. 89, receiving 200r, showed depression to 63% of normal on the 4th day; beginning recovery was noted between the third and fourth week.

Comparison of the two figures shows initial elevation of platelets followed by depression in all four animals. The elevation of platelets was higher and depression of both platelets and white blood cell count was less severe in the shielded animals. Comparison of No. 88 (200r unshielded) and No. 89 (200r with shields) shows a difference in the time and degree of depression. In the unshielded animal, the white blood cell count reached the lowest point (38% of normal on the 18th day; in the unshielded dog, the white blood cell count reached the lowest point (60% of normal) on the 21st day.

Figure 6 A shows the red blood cell count and hemoglobin response in the control animals and figure 6 B showed the response in the animals with partial body shielding. Comparison of response of the two animals receiving 400r, one unshielded and one with partial shielding of bone marrow, shows a striking difference. Autopsy and bone marrow studies were done on the unshielded animal; pathology report: complete aplasia of bone marrow. The shielded animal recovered promptly, indicating that the sparing effect of partial shielding of bone marrow may insure recovery when doses are of this order. All surviving animals recovered promptly and have remained healthy; at no time was there evidence of nausea, vomiting or diminished appetite or activity. The protective effect of shielding could be of obvious importance but this might be masked or exaggerated when the lethal dose of radiation may be influenced by general physical condition, nutritional status and uncertain breed.

Experience of many individuals with irradiation of dogs has resulted in considerable variation in opinion as to the $L.D._{50}$ and $L.D._{100}$. Among the reasons for this are the relatively small number of animals studied, variations in quality of radiation, geometry of irradiation, and methods of measuring and recording exposure dose. The factors of nutrition, general physical condition and breed may further influence the tolerance to radiation. To reduce some of these variables, it is necessary to undertake radiation of control animals, giving particular attention to their nutrition and general health.

Six dogs were selected and prepared for radiation over a period of about 4 weeks. All received inoculations for distemper and rabies and all received an adequate and balanced diet. All animals were kept in quarantine for 9 days and then were placed in semi-quarantine (separate cages) where the remained throughout the period of observation. Preceding irradiation, blood counts were taken daily for one week and every other day thereafter (1 to 2 weeks) until the blood count stabilized and a normal base line was obtained. Three of the animals received 400r and three received 500r total body radiation with 2 m v. All animals survived and all showed a uniform depression of white blood cell and platelet count with recovery beginning about 3 weeks after irradiation and returning to normal at about 7 weeks.

Figure 7 shows the white blood cell count and platelets in 3 animals following 400r total body radiation; figure 8 shows the white blood cell and platelets in 3 animals following 500r total body radiation. In both groups the platelet count dropped sharply (5 to 20% of normal) by the 11th day and remained at this level until recovery began about three weeks after exposure. In the three dogs receiving 400r, white blood cell depression ranged from 8 to 32 per cent of normal; in the 3 receiving 500r, depression ranged from 20 to 28 per cent of normal. In spite of severe depression of both white blood cell count and platelets, there was no evidence of bleeding or infection. No supportive therapy of any kind was offered. Recovery began about the 3rd week and by the 7th week complete recovery was noted in one of the 400r group and in two of the 500r group.

Figures 9 and 10 show the response of hemoglobin, hematocrit and red blood cell count with the expected red cell survival rate. None of these fell below 60 per cent of normal. In both groups the fall in red cell count corresponded roughly with the expected 1 per cent per day decrease, based on red cell life span, until recovery began at about the 3rd week.

This demonstration of the effect of nutrition and general health upon tolerance to radiation is no surprise but the importance may have been under estimated. For critical observations it might be necessary to use pure bred dogs.

The direction of further investigation is to study factors which influence tolerance and recovery such as partial body shielding and bone marrow transplants. Preliminary work must be done on large animals such as dogs or small primates. In determining the factors that influence tolerance and recovery, a firm estimate of lethal dose of radiation is essential and this will require that the factors of nutrition, infection, general health and breed must be considered.

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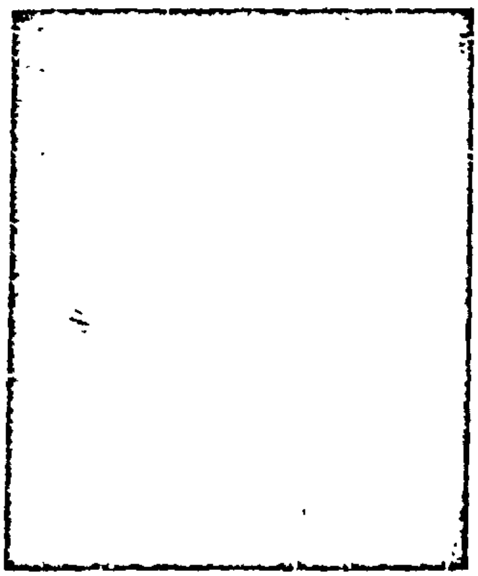
TABLE I

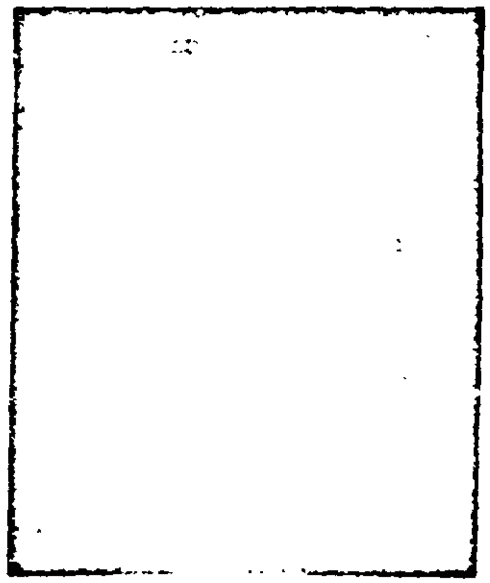
Patient	Diagnosis	Radiotherapy			% RISA Absorption					% RISA Absorption					Remarks
		Date	Daily Dose	Total Dose	Date	0-2 hrs	2-4 hrs	4-6 hrs	24 hrs	Date	0-2 hrs	2-4 hrs	4-6 hrs	24 hrs	
J.B.	Chronic lymphatic leukemia	2-24-58 7-17-58	50 (TBR)	350 (TBR)	3-17-58	10.2	9.0	7.3	3.8	4-30-58	10.7 15.8 16.8 13.2	13.9			
A.A.	Hepatoma	5-13-58 5-14-58	200	400	5-14-58	1.4	2.3	3.0							Deceased
T.T.	Carcinoma of bladder	6-19-58 7-9-58	300	4200	6-19-58	-	10.0	11.0							Did not keep appt.
E.B.	Carcinoma of lung	6-26-58 7-10-58	200	1600	6-25-58	8.0	6.0	4.7		7-10-58	9.0	6.8	6.6		
B.F.	Carcinoma of vaginal cuff	6-26-58 7-17-58	300	4500	6-25-58	11.0	9.0	7.3		7-31-58	26.5	46.1 45.0			
G.C.	Carcinoma of lung	6-26-58 7-30-58	300	6000	6-25-58	9.0	6.6	5.7		8-11-58	13.9	12.0	11.0		
H.A.	Retro-bulbar tumor	7-29-58 8-8-58	250	2300	7-23-58	4.3	4.1			8-18-58	10.2	8.8			
B.R.	Carcinoma of cervix	8-15-58 9-7-58	200	3000	7-23-58	5.8	8.0								Did not keep appt.
H.S.	Carcinoma of cervix	8-18-58 9-10-58	200	3000	7-24-58	5.6	5.1			10-3-58	10.9	10.4			

RISA Absorption From Bowel Before And After Radiation



8-4-58

Fig. 1 A. Chest film showing pulmonary metastases before treatment.



9-29-58

Fig. 1 B. Chest film showing response of pulmonary metastases to total body radiation.

Fig. 2.
Case 1 K.R.

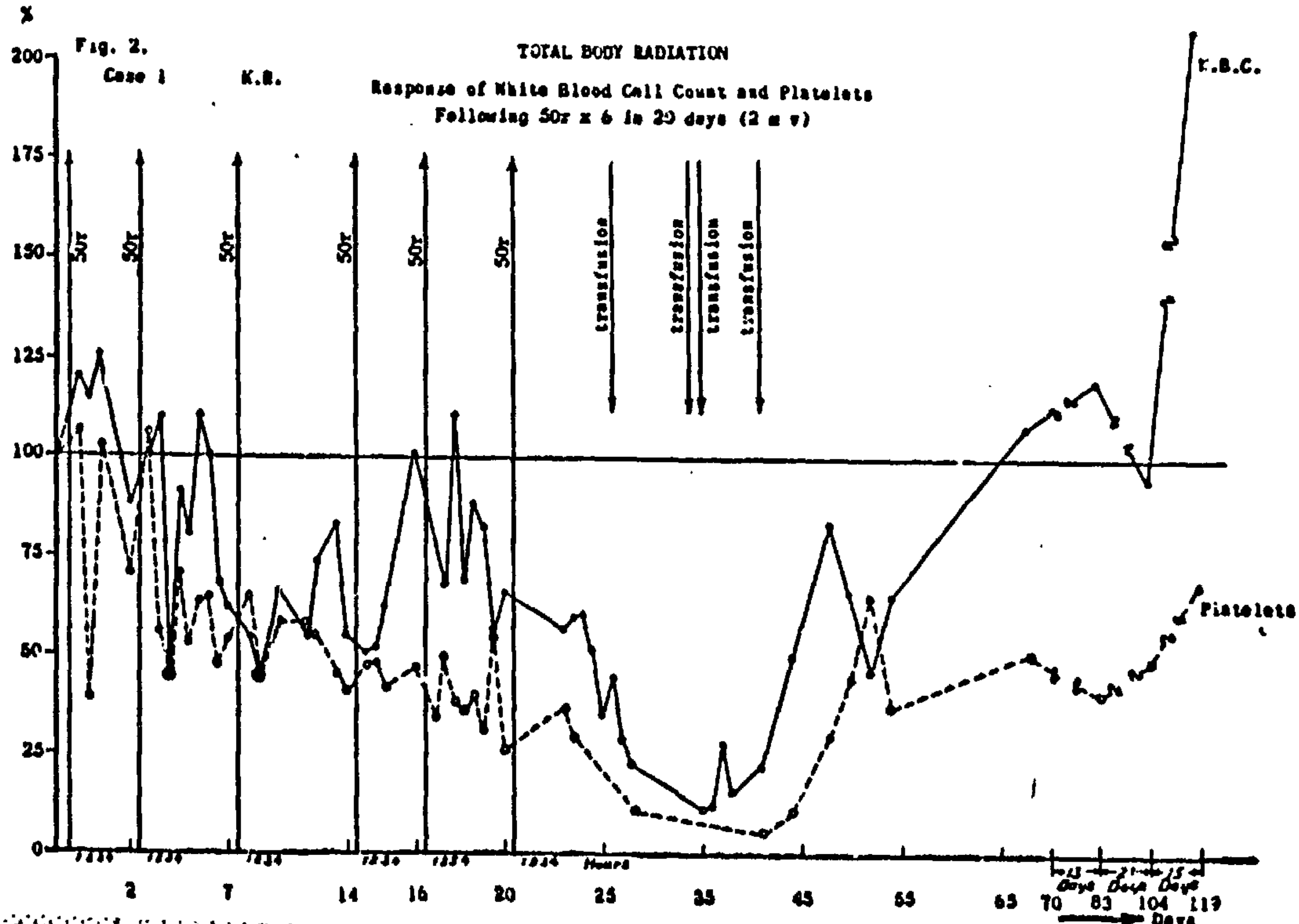


Fig. 3

Case 2. A.S. LARGE FIELD AND TOTAL BODY RADIATION
Response of Peripheral Blood Count

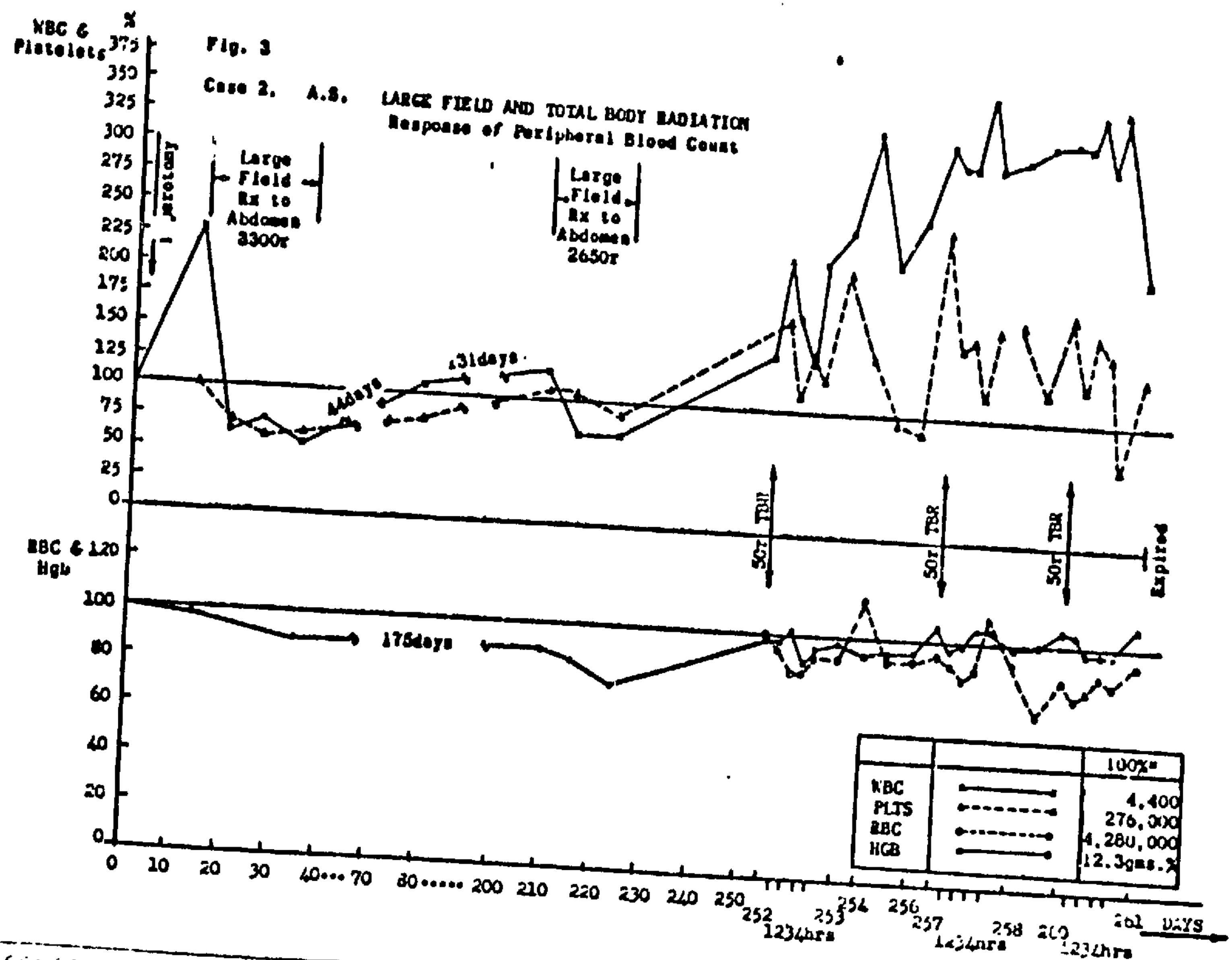


Fig. 4. Distribution of Shields (9 mm. lead) for Protection of Bone Marrow During Total Body Radiation

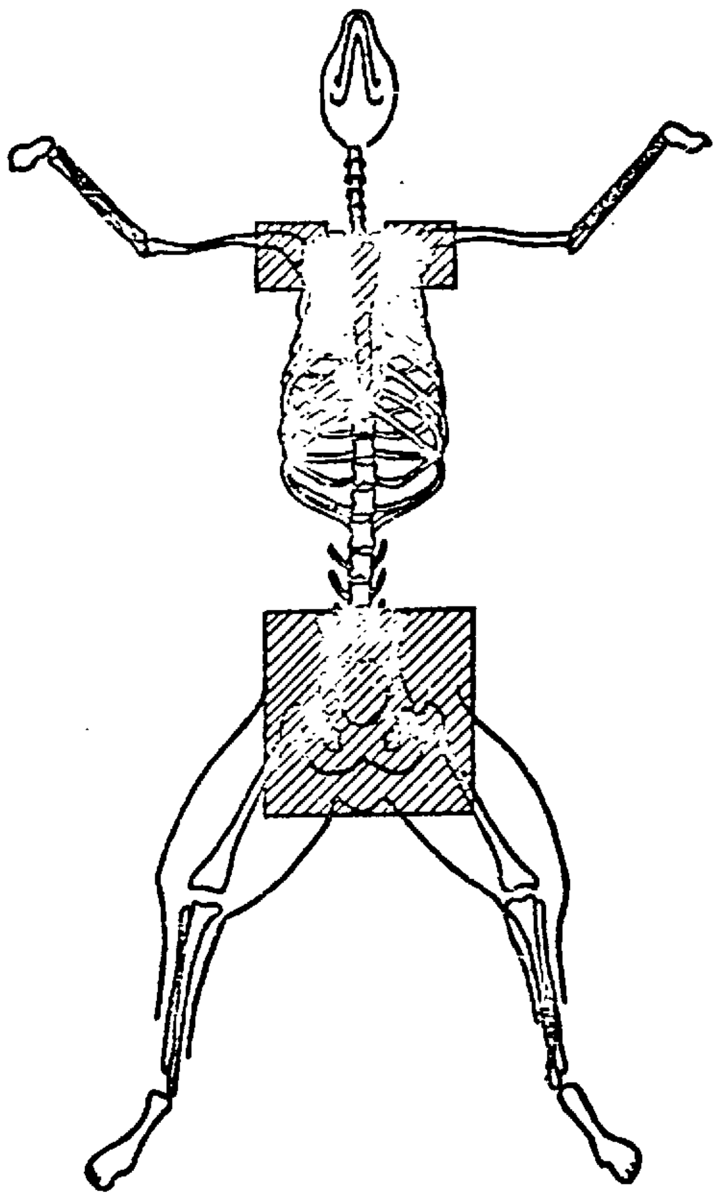


Fig. 5 A.

Response of White Blood Cell Count and Platelets Following Unshielded Total Body Radiation

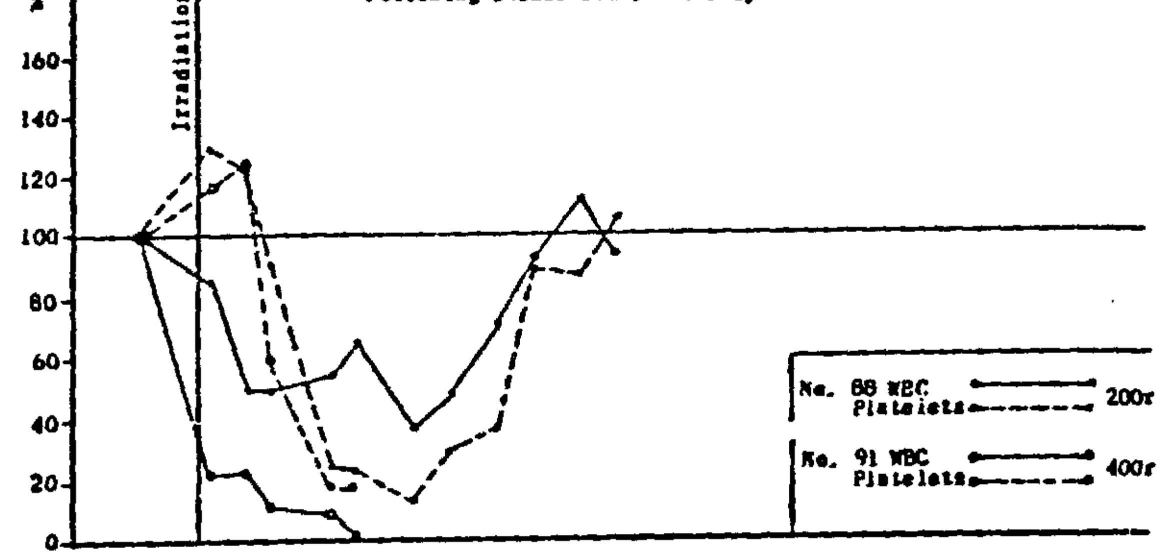
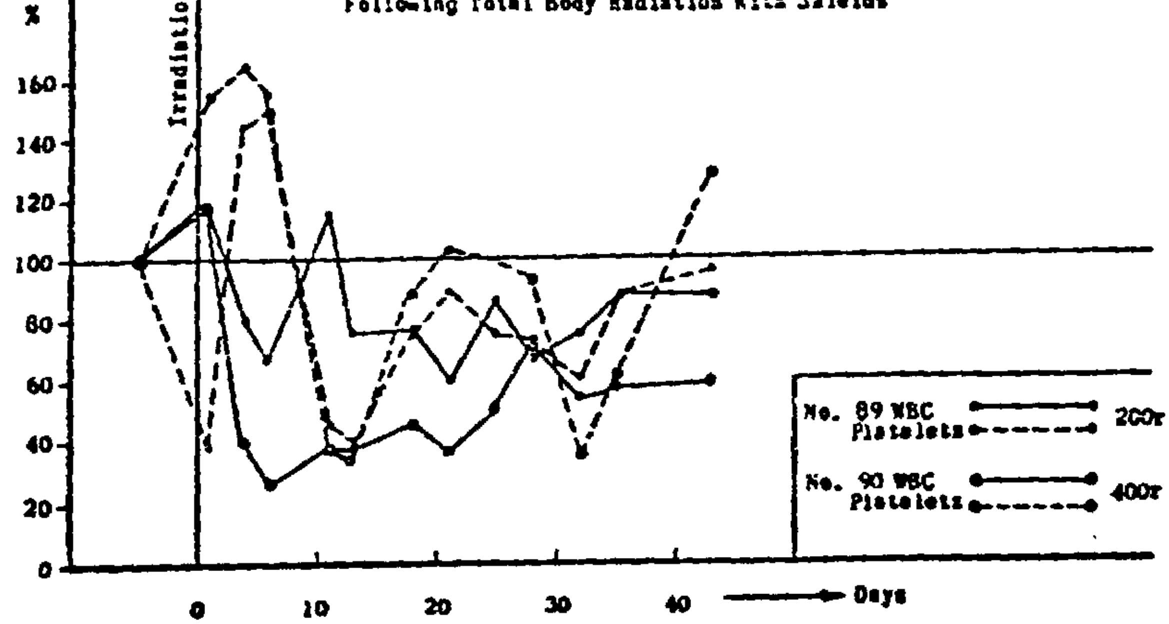


Fig. 5 B.

Response of White Blood Cell Count and Platelets Following Total Body Radiation With Shields



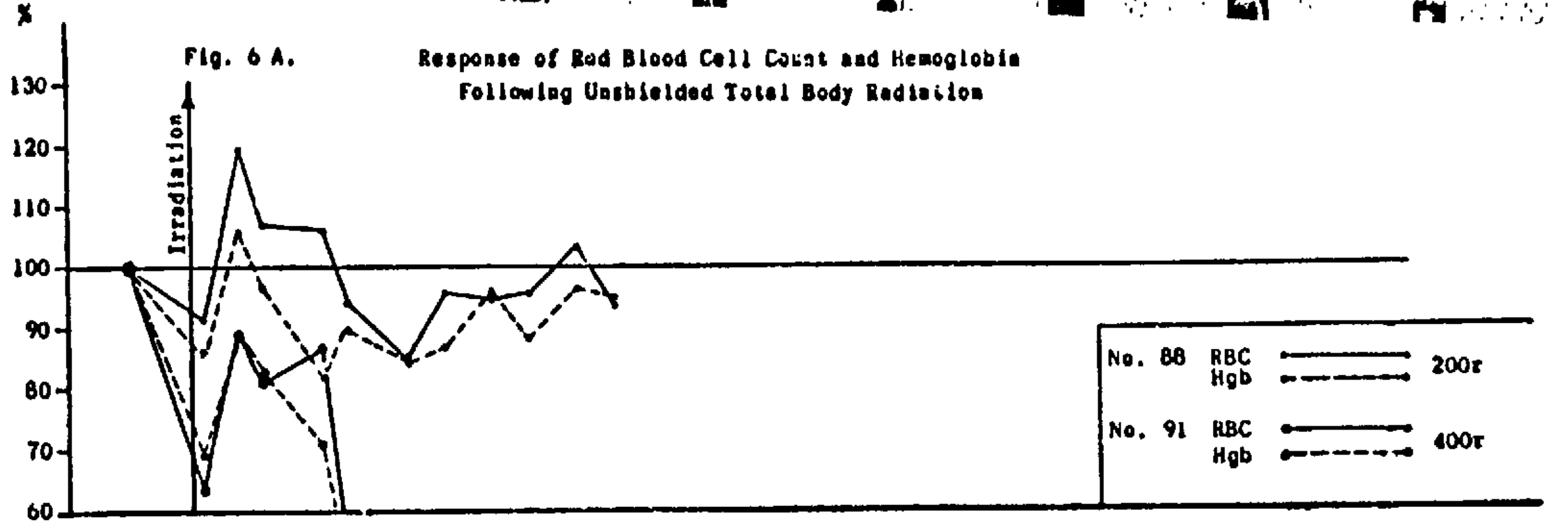


Fig. 6 A.
Response of Red Blood Cell Count and Hemoglobin
Following Unshielded Total Body Radiation
%
130
120
110
100
90
80
70
60
Irradiation
No. 88 RBC
Hgb
200r
No. 91 RBC
Hgb
400r

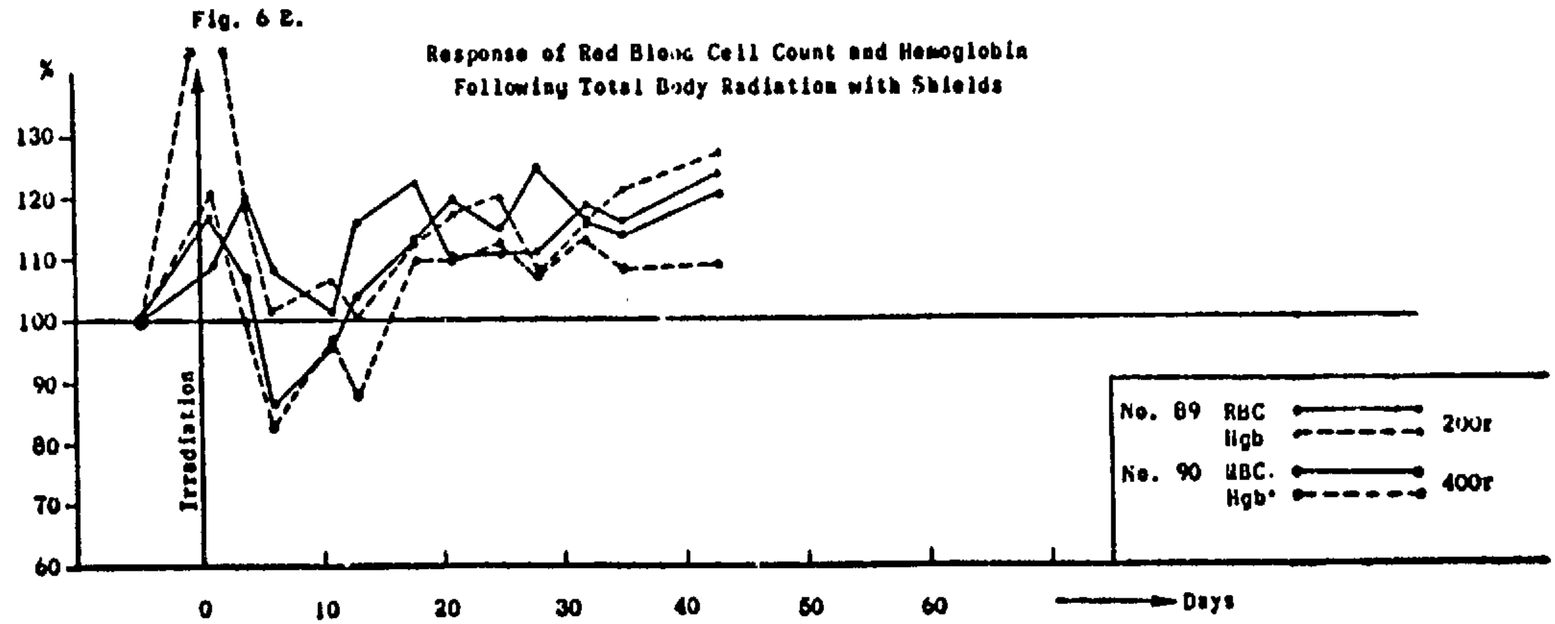


Fig. 6 B.
Response of Red Blood Cell Count and Hemoglobin
Following Total Body Radiation with Shields
%
130
120
110
100
90
80
70
60
Irradiation
0
10
20
30
40
50
60
Days
No. 89 RBC
Hgb
200r
No. 90 RBC.
Hgb
400r

Fig. 7.

TOTAL BODY RADIATION
Response of White Blood Cell Count and Platelets
in 3 Dogs Receiving 400r

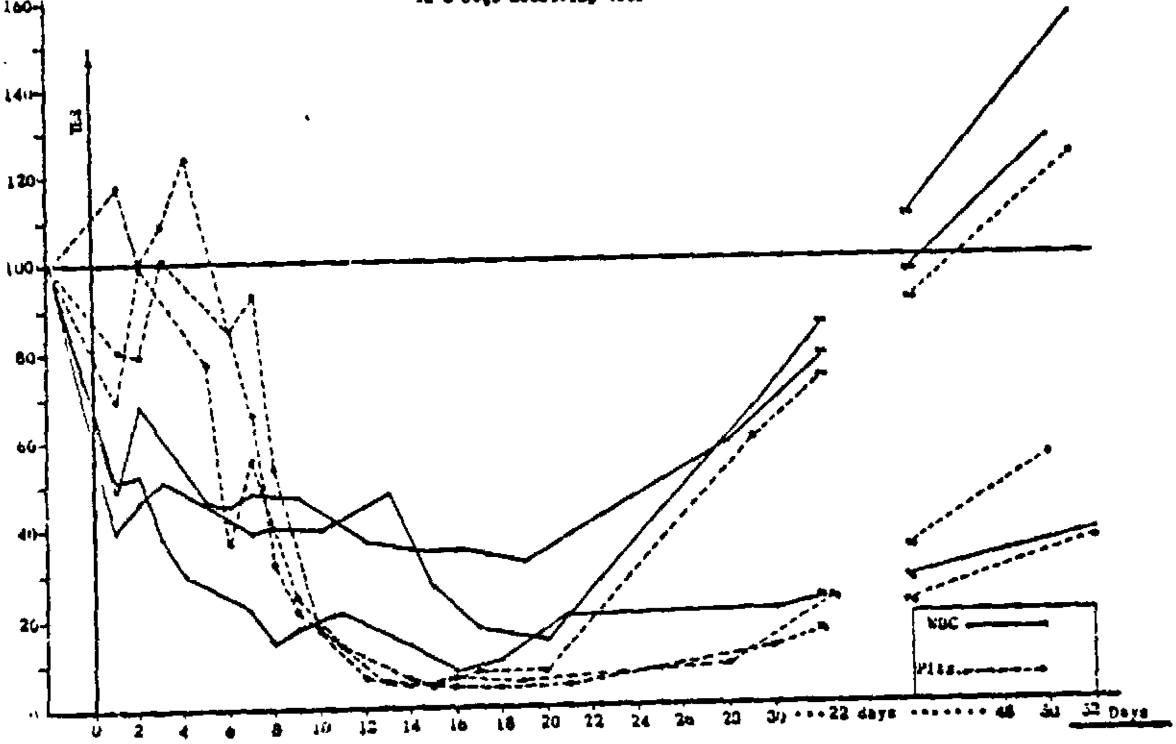


Fig. 8.

TOTAL BODY RADIATION
Response of White Blood Cell Count and Platelets
in 3 Dogs Receiving 500r

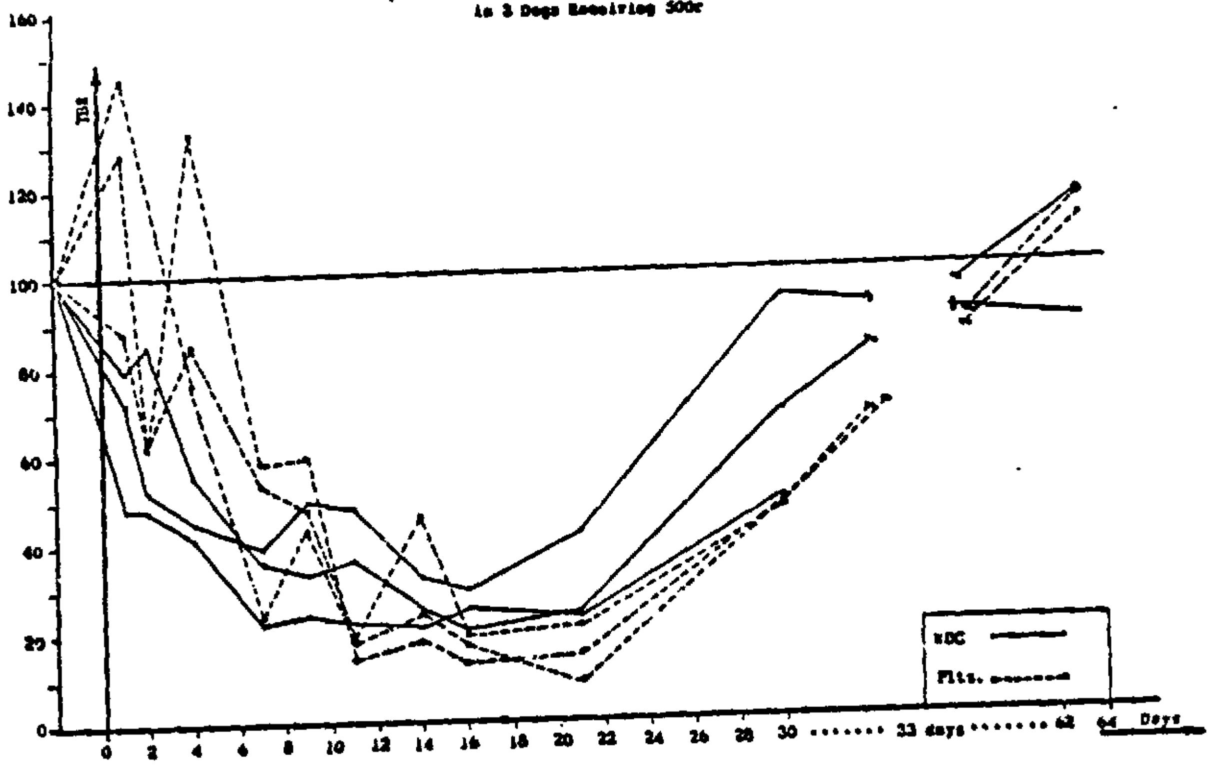


Fig. 9.

TOTAL BODY RADIATION

Response of Red Blood Cell Count, Hemoglobin and Hematocrit in 3 Dogs Receiving 400r

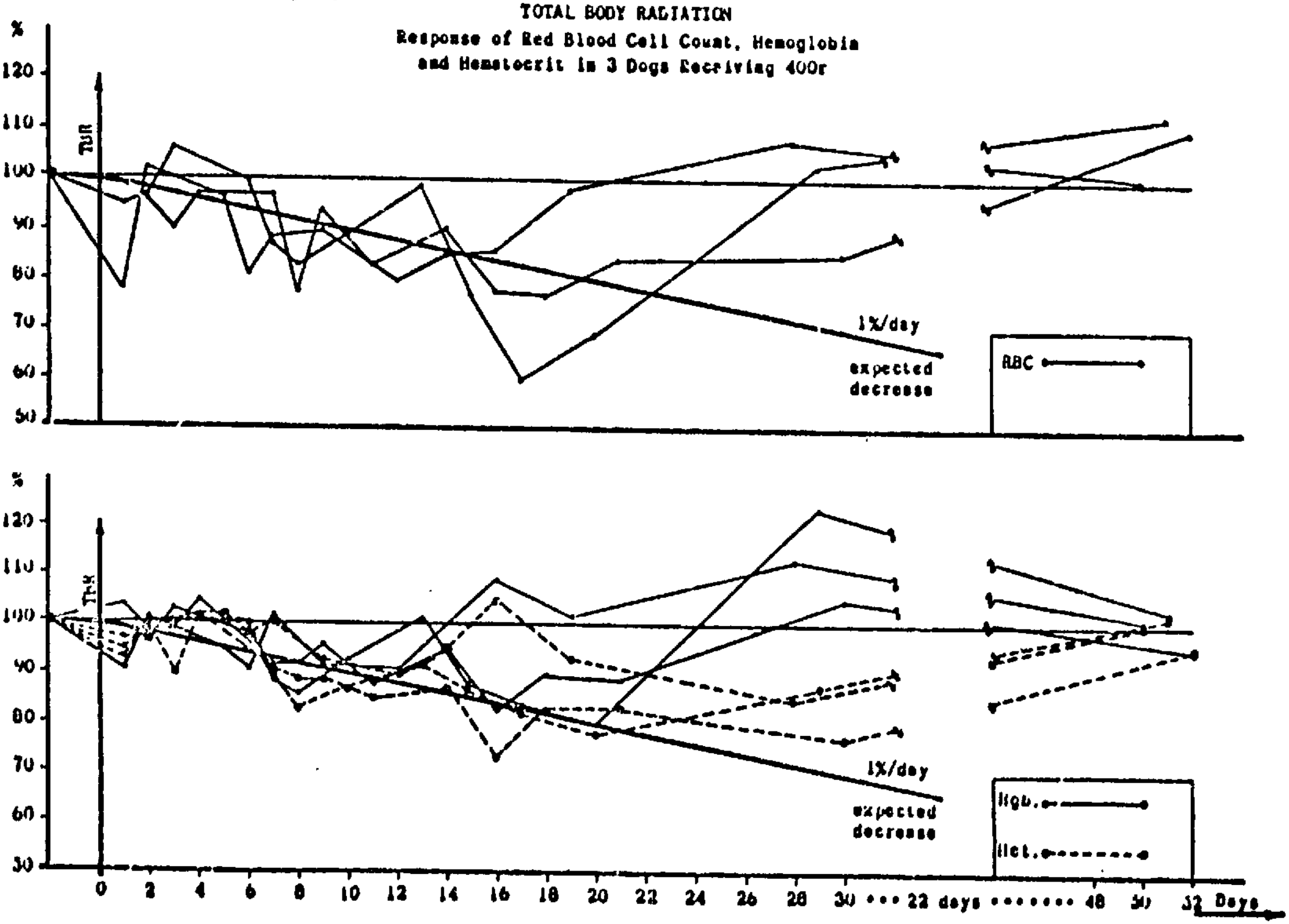
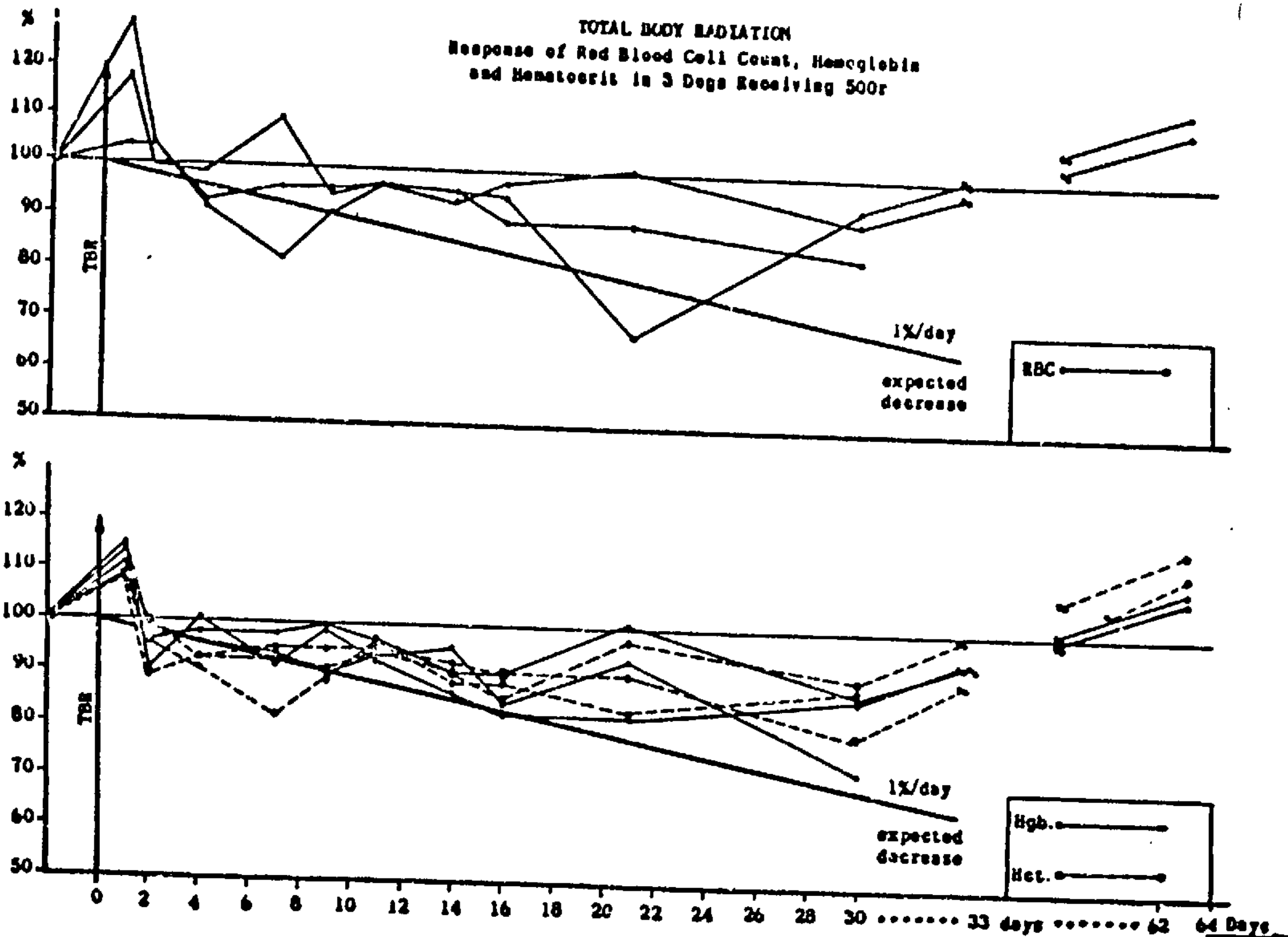


Fig. 10

TOTAL BODY RADIATION
Response of Red Blood Cell Count, Hemoglobin and Hematocrit in 3 Dogs Receiving 500r



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