FINAL REPORT

TO THE

DEPARTMENT OF THE ARMY

ARMED FORCES SPECIAL WEAPONS PROJECT

Contract No. DA-49-007-MD-755

STUDY OF THE POST-IRRADIATION SYNDROME IN HUMANS

Date of Report: February 1, 1958

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Final Report
Dr. Nickson
MD-755

Introduction:

This report will be divided into four sections: I- Hematology and clinical findings, II- Lipoprotein studies, III- Electrolyte and metabolic studies, IV- Future plans.

Selection of Patients

All patients given total body irradiation had disseminated cancer; however, the criteria for the selection of suitable cases were severe so that the patients were as near as possible to the physiological norm. A detailed list of these criteria was included in last year's report.

Method of Irradiation

All external irradiations were accomplished with the 1 Mevp G.E. Resonant generator using exposure ports: upper and lower halves of the body, anterior and posterior. The upper and lower fields were separated by 5 cm. to compensate for the penumbra and the divergence of the beam. This results in a fairly uniform dose throughout the body. All doses are expressed as air doses, measured at the mid-plane of the body. The mid-plane was 290-300 cm from the x-ray target. The dose rate was 5-6 r/min.

In collaboration with Drs. Bond, Cronkhite, and Robertson at the Brookhaven National Laboratory, one patient was given 18 mc of Na^{24} by mouth for an estimated mid-plane body dose of 50 r.

I. Hematological data and case reports

Hematological data on all patients are presented in Table I and Figures 1-13.

Case Reports

Patient M. W. received 18 mc of Na^{24} for a calculated mid-plane dose of 50 r. This 50 year old white female had had a cancer of the base of the tongue with no evidence of residual disease and also had a carcinoma of the esophagus with regional metastases. Liver function studies and blood counts were within normal limits. No symptoms resulted from the total body irradiation. Pre-irradiation platelet counts averaged about 225,000 and showed very little change until the 20th day post-irradiation when they began to fall, reaching a minimum on the 27th day post-irradiation when the count was 116,000. By the 30th day post-irradiation the platelet count had risen to 177,000 and the patient was discharged from the Brookhaven hospital. Subsequent counts in the laboratory were somewhat lower and probably result from differences in techniques of counting. By the 169th day post-irradiation, the platelet count had returned to 222,000. No pronounced leukopenia was observed. There was a slight anemia of 10.0 gms of Hgb around the 40th day (control 13.0 gms) with a gradual increase to 11.4 gm % on the 141st day. Hematological data are summarized in Table I. The patient showed no adverse effects from the procedure. There has been little advance in her neoplastic process. There was no clinical evidence of bleeding. It is anticipated that the patient will be given a second course of radiation in the near future. She was admitted to Brookhaven National Laboratory Hospital on October 21, 1957 and is having baseline studies performed in preparation of a second course of total body irradiation.

Patient H.S. had a primary carcinoma of the cervix with pulmonary and pleural metastases. Prior to total body irradiation with 150 r in air at the mid-plane with 1 Mevp x-rays, liver function studies and blood counts were within normal limits. The control white blood count was about 11.3 x 10^3/cu. mm. and it fell steadily until the 34th day when it reached a minimum of 3.3×10^3/cu. mm. From this time on it rose slowly to 7.0×10^3/cu. mm., but it never returned to control value. By the third day, the lymphocytes fell to about one-half of the control value. Platelet counts showed little change from the control values of 3.5×10^5/cu. mm. until about the 14th day when they began to drop, reaching a minimum of $.435 \times 10^5$/cu. mm. on the 27th day. By the 59th day they had returned to 2.34×10^5/cu. mm. There was evidence of clinical bleeding in the form of petechiae and ecchymosis between the 25th and 30th day. The patient had some transitory nausea following irradiation but no vomiting or diahrrea. Graphs of the hematological response are attached as figures 10 to 13. The pleural and pulmonary metastases became a serious problem about 40 days post total body irradiation. It was necessary to initiate palliative radiotherapy to the left chest at this time. She received 1815 r TD to left chest in 14 days.

Patient L.G. had a malignant melanoma of the left leg with widespread metastases in that extremity only. She received 150 r in air to the mid-plane of the body delivered by the 1 Mevp x-ray machine. She experienced no nausea, vomiting or diahrrea. The hematological response followed the same pattern as that of the previously reported cases. The platelet count was 2.57×10^5/cu. mm. prior to irradiation and began to fall about the 12th day post-irradiation when it was 2.3×10^5/cu. mm and it reached a minimum of 0.28×10^5/cu. mm. on the 28th day. It increased steadily from this point on, reaching 3×10^5/cu. mm. on the 56th day. Granulocyte counts paralleled the total white count and the lymphocytes showed the usual prompt drop to about one-half of the control value with a slow and incomplete recovery. Details are shown in the attached graphs, figures 1 to 5.

One patient (C.H. previously reported as K.H.) deserves special attention. She had a primary carcinoma of the stomach which was not resectable as proven by exploratory laparotomy. On December 19, 1955 she received 150 r total body irradiation. Radiation treatment of the primary lesion was started on February 7, 1956 with the cobalt 60 apparatus. She received a tumor dose of 5000 r in 5 weeks. The patient did extremely well until June 5, 1957 when pelvic metastases were found. The patient had minimal symptoms from these lesions and was in excellent general health. On July 1, 1957 she received a second course of total body irradiation up to a dose of 75 r in air. Forty-one days post total body irradiation, therapy was started to the pelvis. She received 4400 r tissue dose in 32 days. This treatment was completed on September 20, 1957. The attached graphs figures 6 to 9 summarize the hematological findings following the second course of total body irradiation. The hematologic changes of the prior course of total body irradiation are also shown in these figures.

It is interesting to note that the response to 75 r as a second course of radiation resulted in an initial drop in the WBC which, however, was not as profound nor as prolonged as with the initial total body irradiation of 150 r. The platelet depression which we have seen between the 20th and 35th day with 150 r did not occur with the second course of irradiation. However, the lymphocyte count fell as rapidly and steeply with the second irradiation and it appeared to remain depressed for the entire 100 days observation.

There was no evidence of bleeding at any time and bleeding and clotting time remained within normal limits. Bone marrow aspiration before the first total body irradiation was reported as rather hypocellular and appeared to be diluted with peripheral blood. What marrow elements were seen appeared "normal" and prior to the second course, the report stated: "marrow appears fatty and hypoplastic in some areas, in others it is adequately cellular with all cell elements represented, with increased numbers of cells of the erythroid series."

Since institution of pelvic irradiation there has been a progressive anemia and thrombocytopenia. This patient has been re-admitted to the hospital for investigation of possible sites of bleeding, and to evaluate the status of the bone marrow.

II. <u>Lipoprotein studies</u>

Lipoprotein studies as previously described were carried out on one patient (L.G.). At the time of the maximum thrombocytopenia there was a marked increase (+++) in the amount of clearing factor. This persisted, even after the platelet count had risen above 200,000. At the time of the greatest thrombocytopenia there were petechiae. This observation was consistent with earlier ones, viz. that there has been an increase in clearing factor in all patients that showed clinical evidence of bleeding. Patients who have not had clinical evidence of bleeding have shown no increase in clearing factor; however they have had severe thrombocytopenias.

Shifts of emphasis in the lipoprotein research program within the Institute have resulted in the discontinuation of this facet of the investigation. The professional personnel and equipment formerly available to this phase of our project are now being fully utilized in other studies.

III. Electrolyte studies

The common electrolyte abnormalities occurring after irradiation have been outlined, and appropriate therapies have been established (1). These are potassium depletion alkalosis from inanition, hypochloremic alkalosis from vomiting, and hyperchloremic acidosis from diarrhea. In addition to these, adrenal insufficiency, ammonia toxicity, and hyperkalemia may be seen on occasion.

Potassium spaces have been studied pre- and post-irradiation. Such data are being analyzed by an analogue computor to see if there is any difference in the various body compartments into which potassium goes. Preliminary data suggest that there may be differences in the very early portion of the fall-off curve.

The CNS death modality in dogs has been studied from the physiological point of view. It has been shown that the convulsive phase of this syndrome is associated with a respiratory alkalosis (2). This work is being continued. Pathological examination of the irradiated brains is being done in collaboration with the Pathology Department of Cornell University Medical College.

IV. Future plans

Careful and detailed dosimetry will be done utilizing total body phantoms. These will be designed to measure integral dose by means of chemical detectors. A phantom has been designed which contains a complete skeleton. This will permit measurement of dose at any point that is considered to be of biological importance.

Hematological studies will be continued, and additional work will be done on enzymes associated with the clotting mechanism.

Potassium spaces will be studied pre- and post-irradiation with particular emphasis on the immediate fall-off curve. Glucose tolerance curves will also be determined. Further work is anticipated on mechanisms of the super-lethal death in dogs.

Some patients will receive total body irradiation by means of internal isotopes to see if there is any difference in response to a more protracted exposure. It is hoped that more patients can be given two courses of total body irradiation to see if there is a difference in response to the second exposure.

Total exchangeable potassium and the rates of exchange of K^{42} with the various compartments of the body fluids will be studied pre- and post-irradiation with particular emphasis on the early segments of the plasma pale-off curve. Calculations of total glucose increment and the glucose disappearance constant from I.V. glucose tolerances curves pre- and post-irradiation will also be determined. It is anticipated that urinary metabolite excretion patterns will be followed in the next patients receiving total body irradiation. Further work is planned on the mechanism of the super-lethal death in dogs.

BIBLIOGRAPHY

(1) Bane, H. N., Glicksman, A. S., and Nickson, J. J. Common electrolyte problems in radiation therapy. Am. Journal of Roentgenology, in press.

(2) Bane, H. N., Whitehouse, W. L., and Nickson, J. J. Physiological changes in the acute radiation syndrome in dogs. Radiation Research Meeting, 1956.

Table I

PATIENT M.W.: HEMATOLOGICAL DATA, PRE- AND POST-IRRADIATION

	Days, Pre- and Post-Irradiation								
	-15	-12	-9	-5	-2	2	5	8	12
Hemoglobin	13.0								
RBC (1,000,000)									
WBC (1,000)	4.1	5.4	4.9	8.8	6.4	4.7	5.2	3.9	6.9
Polynuclear fil.	61								
Polynuclear non-fil.									
Eosinophiles	6								
Basophiles									
Monocytes	5								
Lymphocytes	28								
Hematocrit	38.8	35.5	34.8	35.5	37.2	34.3	36.2	35.0	35.0
Platelets (1,000)	253.8	212.5	227.5	250.0	261.3	296.3	225.0	332.5	252.5

Days 16 - 33 (continued)

	Days, Post-Irradiation								
	16	20	23	26	27	28	29	30	33
Hemoglobin									10.8
RBC(1,000,000)									3.7
WBC (1,000)	6.0	5.4	4.8	4.9					4.7
Polynuclear fil.	68								72
Polynuclear non-fil.	4								8
Eosinophiles	5								6
Basophiles	2								1
Monocytes	11								4
Lymphocytes	10								9
Hematocrit	35.5	32.6	37.0	36.0				34.4	
Platelets (1,000)	225.0	231.2	130.0	128.8	116.3	142.5	147.5	177.5	125.8

(Continued on next page)

Table I
(Continued)

PATIENT M.W.: HEMATOLOGICAL DATA, PRE- AND POST-IRRADIATION

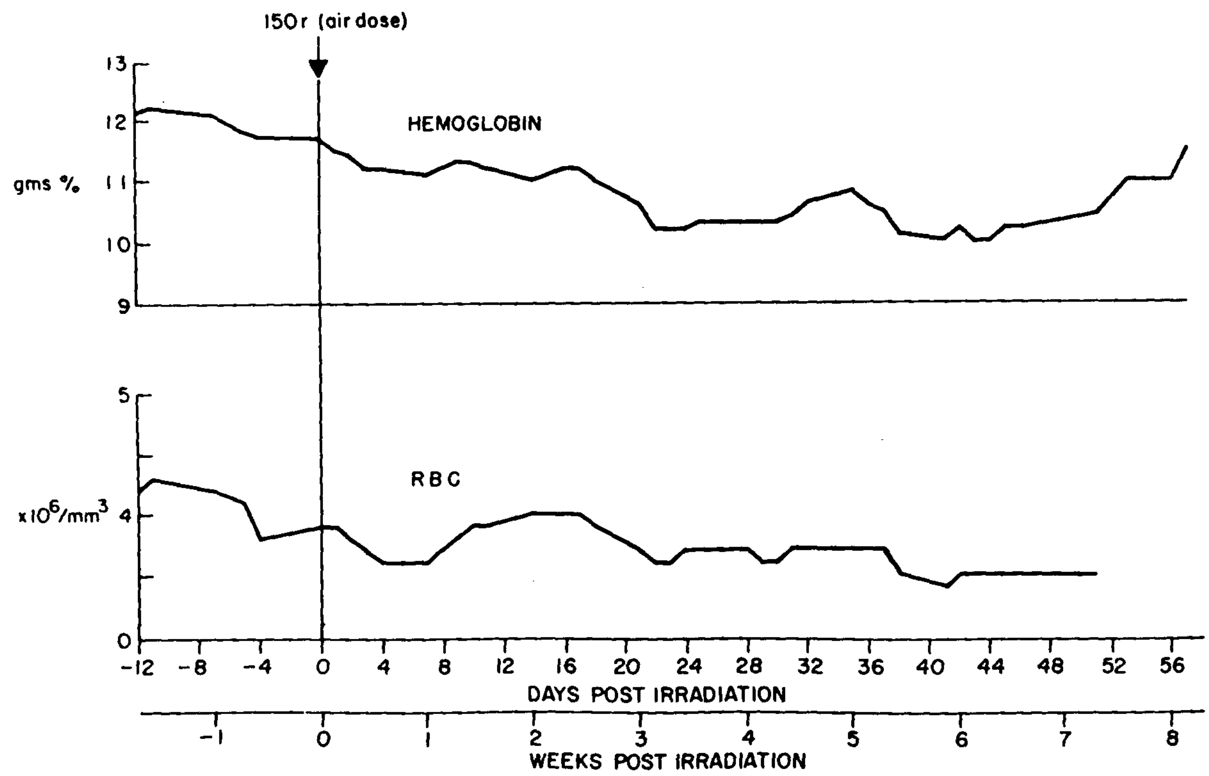
	Days, Post-Irradiation							
	36	40	43	47	54	57	61	71
Hemoglobin	10.2	9.9	10.8	10.6	10.8	10.8	10.9	10.8
RBC (1,000,000)	3.5	3.3	3.3	3.1	3.8	3.6	3.6	3.6
WBC (1,000)	4.7	4.4	3.1	2.9	3.4	4.3	4.5	4.0
Polynuclear — fil.	77	67		77	77	79	81	80
Polynuclear — non-fil.	5	2		2	3	2	2	3
Eoisnophiles	1	2		1	1		1	3
Basophiles	1	1		1				
Monocytes	6	8		3	5	6	8	7
Lymphocytes	10	20		16	14	13	8	7
Hematocrit								
Platelets (1,000)	123.0	125.4		124.0	133.0	126.0	133.2	148.0

Days 85 - 169 (continued)

	Days, Post-Irradiation				
	85	99	127	141	169
Hemoglobin	11.2	11.1	11.3	11.4	10.9
RBC (1,000,000)	3.7	3.7	3.8	3.5	3.7
WBC (1,000)	4.5	5.0	4.9	4.2	6.3
Polynuclear — fil.	84	82	81	76	78
Polynuclear — non-fil.	1	2	3	5	4
Eosinophiles	3	2	1	1	2
Basophiles			2		
Monocytes	2	4	6	8	7
Lymphocytes	10	10	7	10	8
Hematocrit					
Platelets (1,000)	140.4	162.8	167.2	196.0	222.0

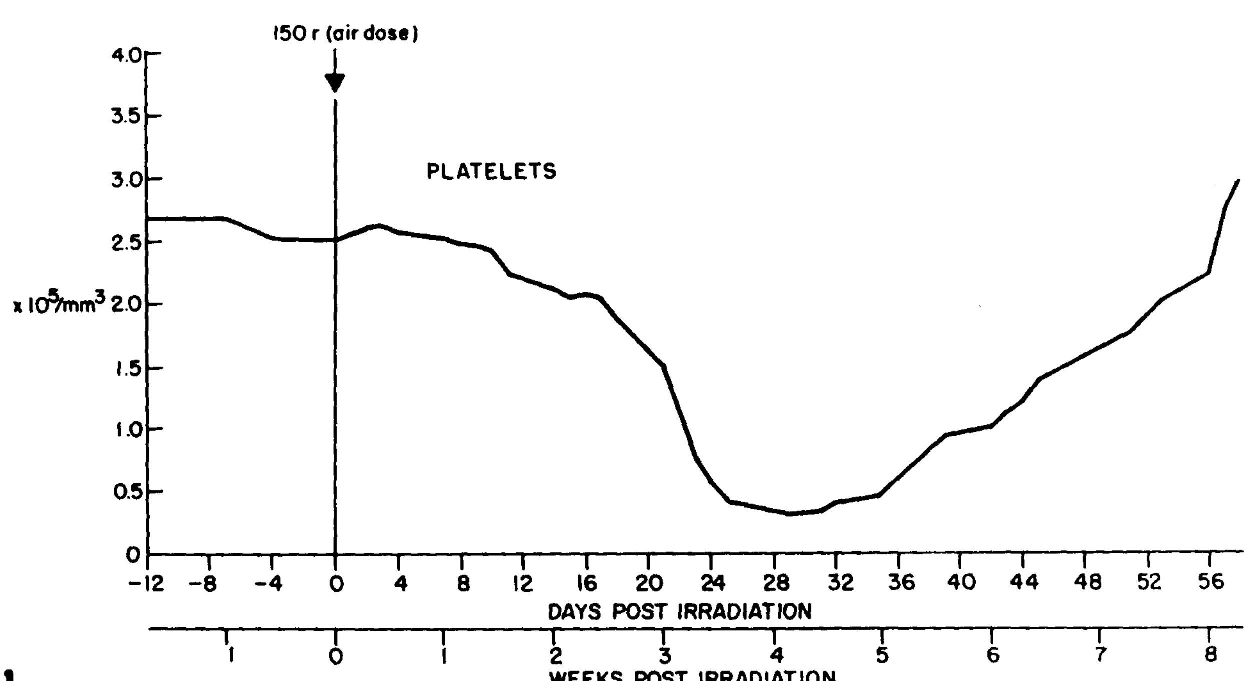
1

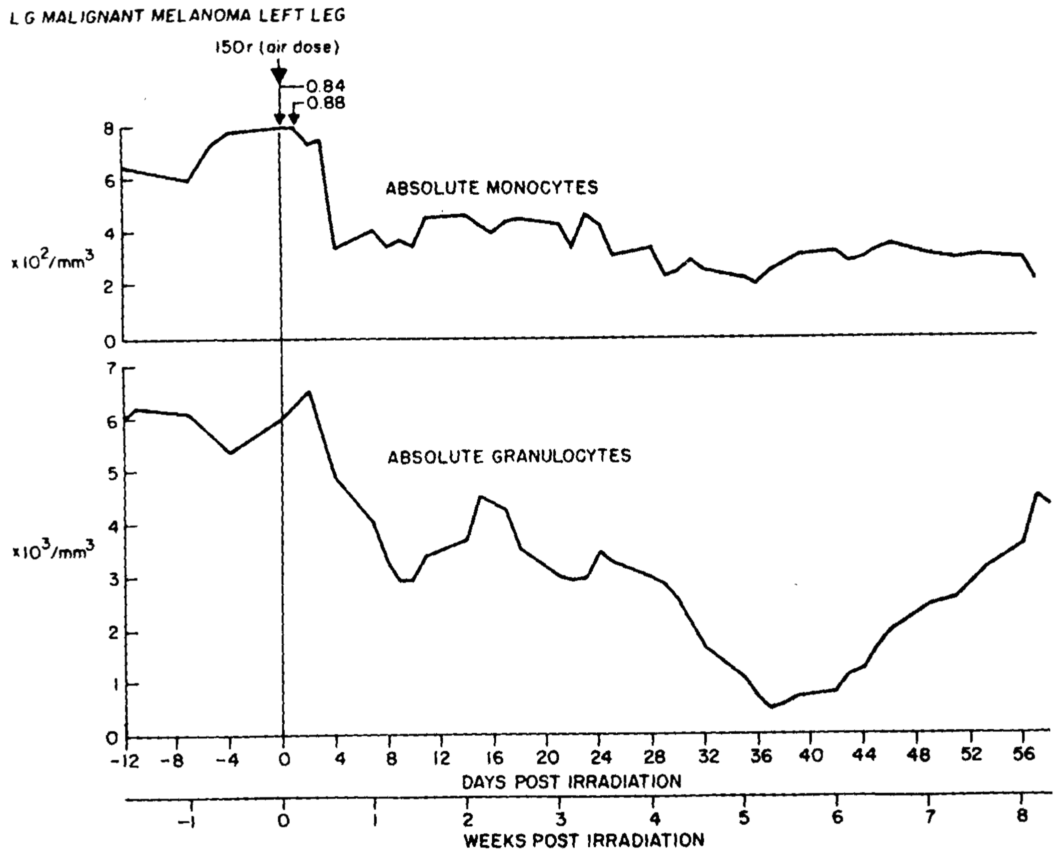
L G MALIGNANT MELANOMA LEFT LEG

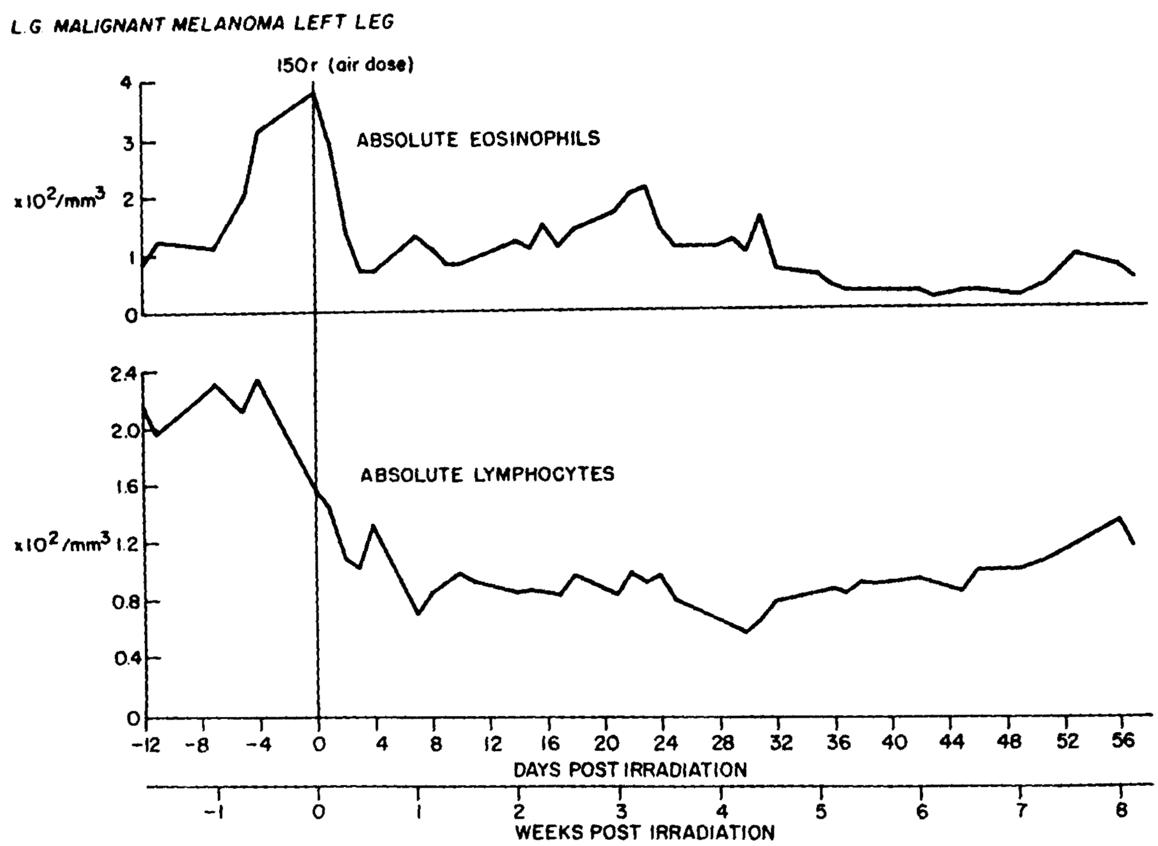


2

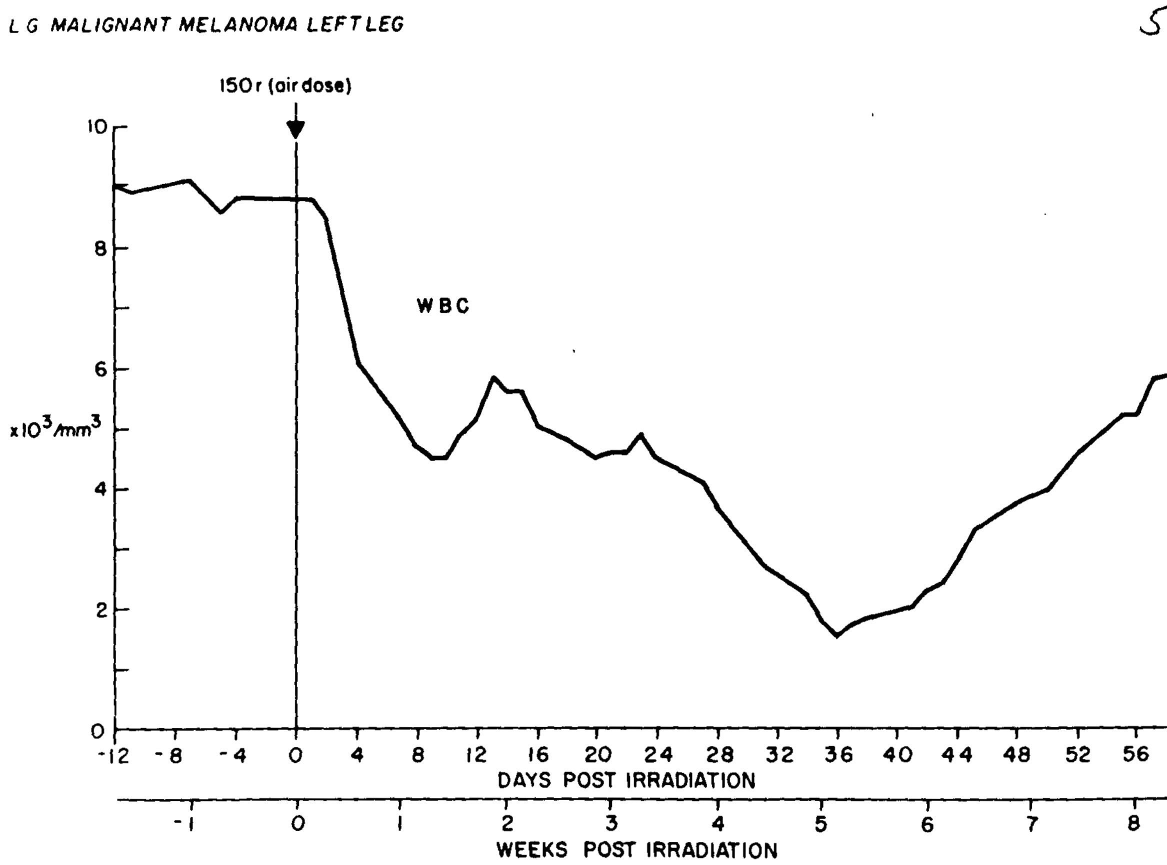
L.G. MALIGNANT MELANOMA LEFT LEG

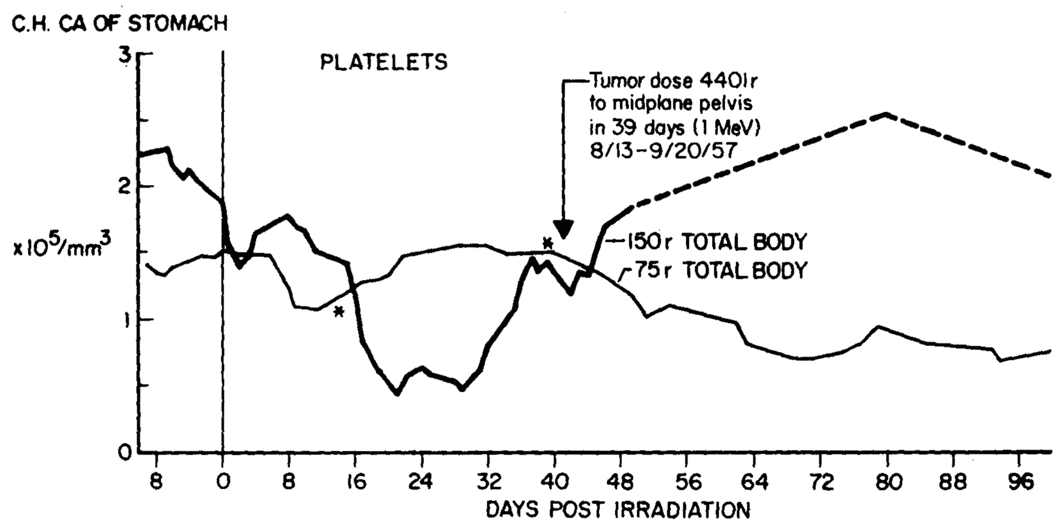



L G MALIGNANT MELANOMA LEFT LEG
150r (air dose)
0.84
0.88
ABSOLUTE MONOCYTES
x10²/mm³
ABSOLUTE GRANULOCYTES
x10³/mm³
DAYS POST IRRADIATION
WEEKS POST IRRADIATION

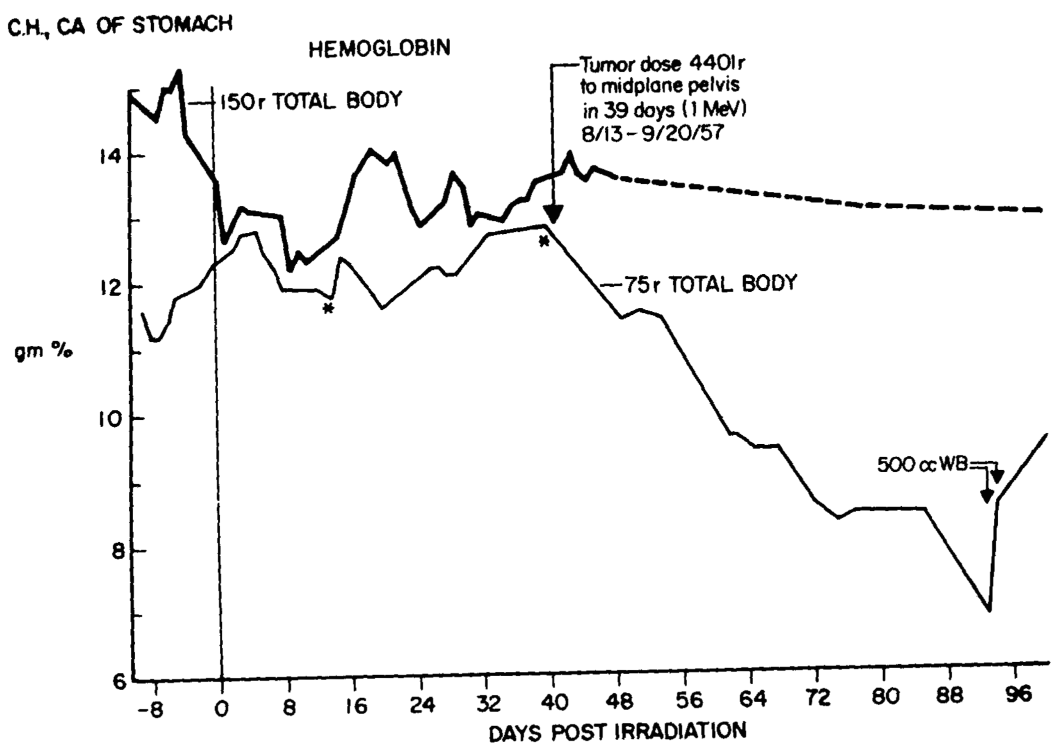

L G MALIGNANT MELANOMA LEFT LEG
150r (air dose)
ABSOLUTE EOSINOPHILS
x10²/mm³
ABSOLUTE LYMPHOCYTES
x10²/mm³
DAYS POST IRRADIATION
WEEKS POST IRRADIATION

5

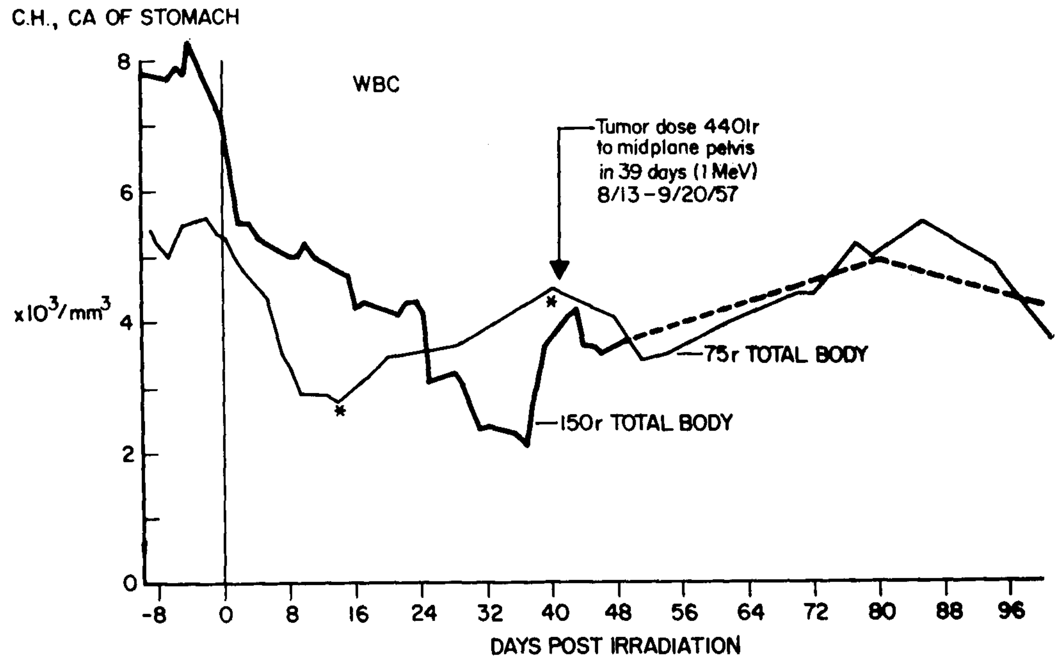

L G MALIGNANT MELANOMA LEFT LEG
150 r (air dose)
WBC
x10³/mm³
10
8
6
4
2
0
-12 -8 -4 0 4 8 12 16 20 24 28 32 36 40 44 48 52 56
DAYS POST IRRADIATION
-1 0 1 2 3 4 5 6 7 8
WEEKS POST IRRADIATION


C.H. CA OF STOMACH
PLATELETS
x10^5/mm^3
Tumor dose 4401r to midplane pelvis in 39 days (1 MeV) 8/13-9/20/57
150r TOTAL BODY
75r TOTAL BODY
3
2
1
0
8
0
8
16
24
32
40
48
56
64
72
80
88
96
DAYS POST IRRADIATION

7

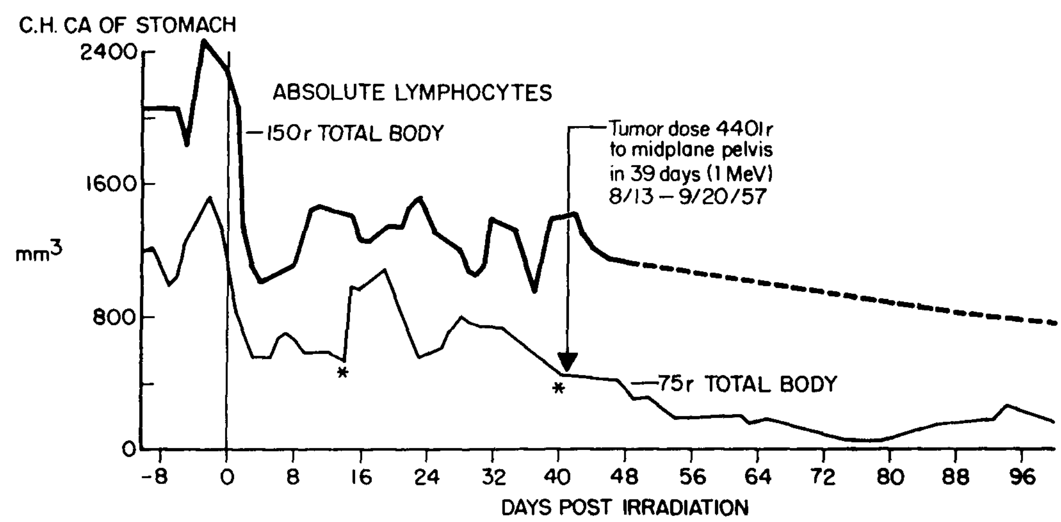

C.H., CA OF STOMACH
HEMOGLOBIN
150r TOTAL BODY
Tumor dose 4401r to midplane pelvis in 39 days (1 MeV) 8/13-9/20/57
75r TOTAL BODY
gm %
500 cc WB
14
12
10
8
6
-8
0
8
16
24
32
40
48
56
64
72
80
88
96
DAYS POST IRRADIATION

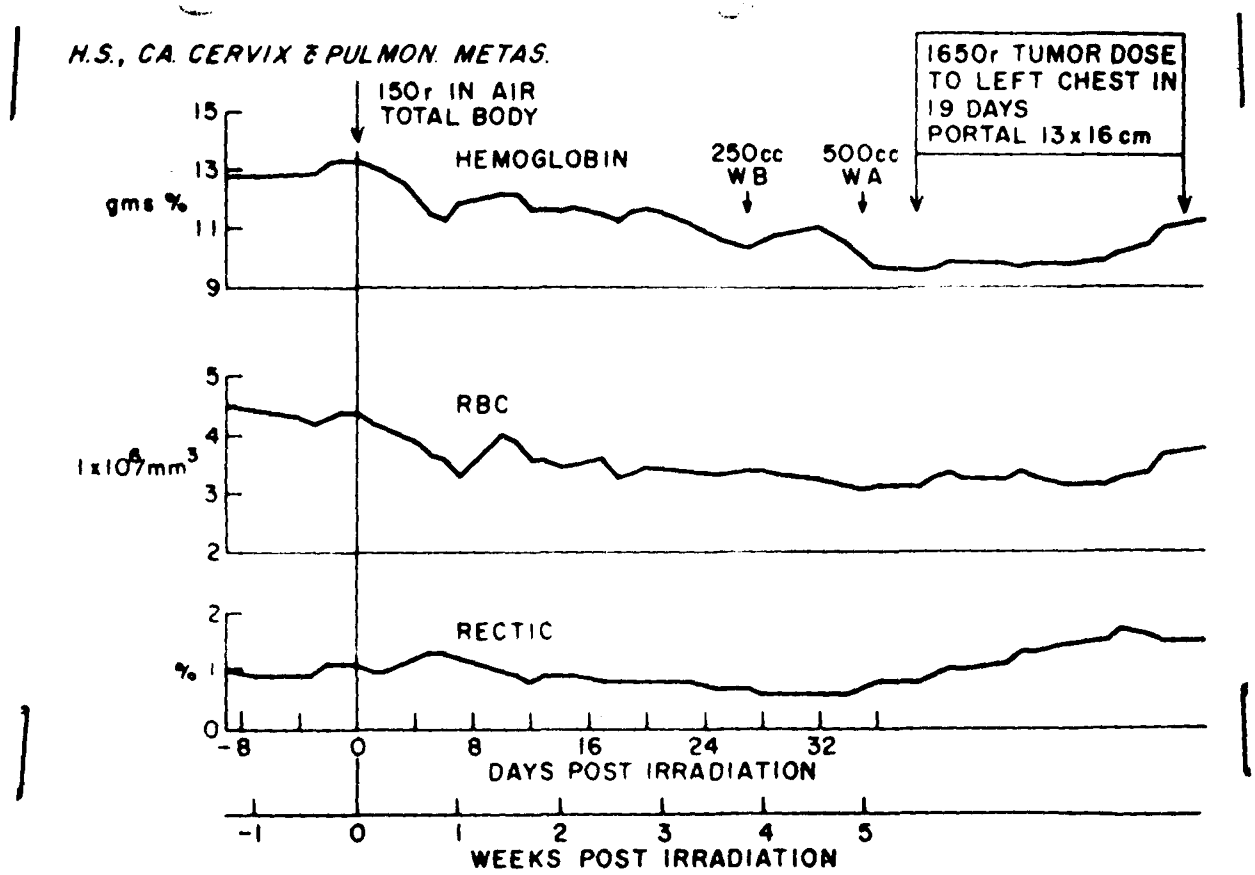
8

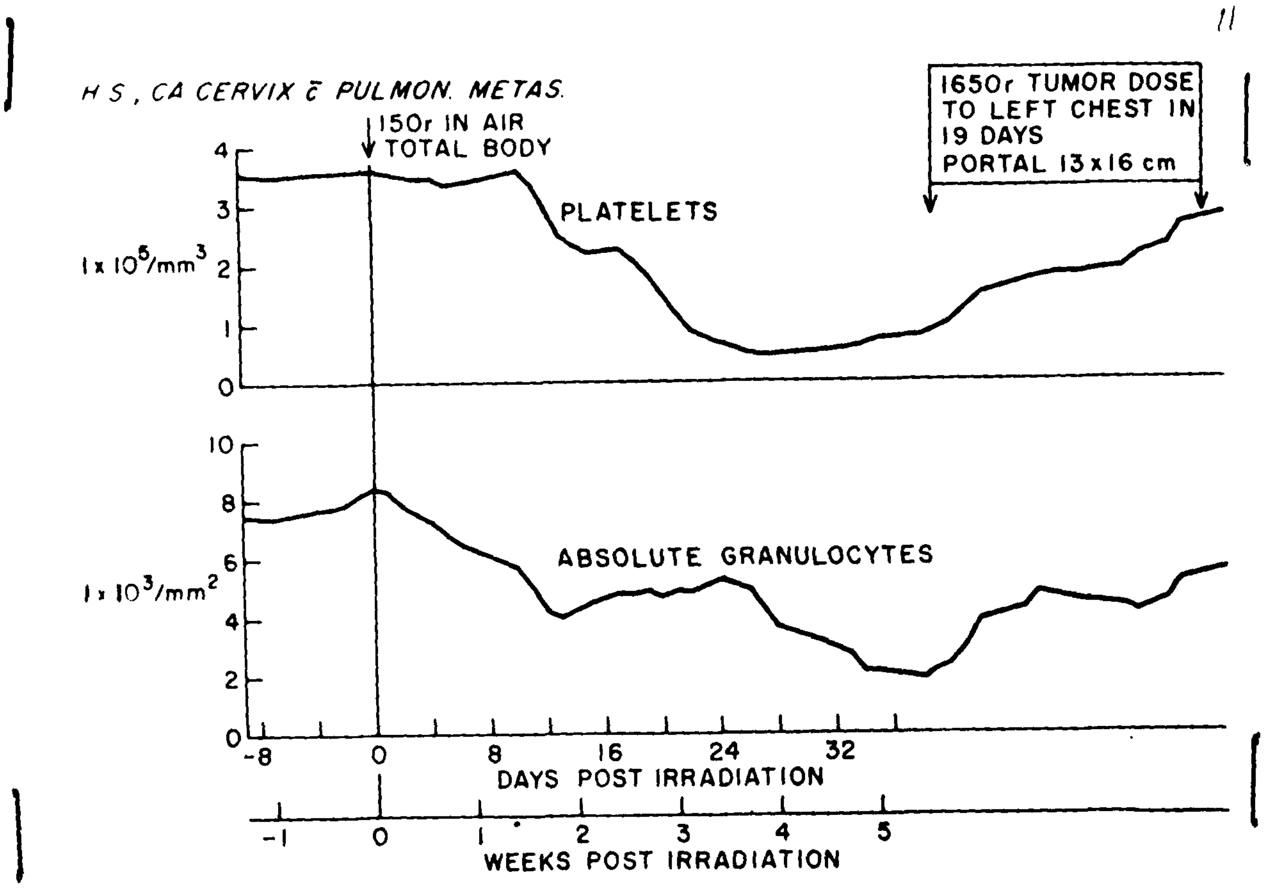


* Determinations between asterisks on 75r plot done by hematology laboratory other than our own

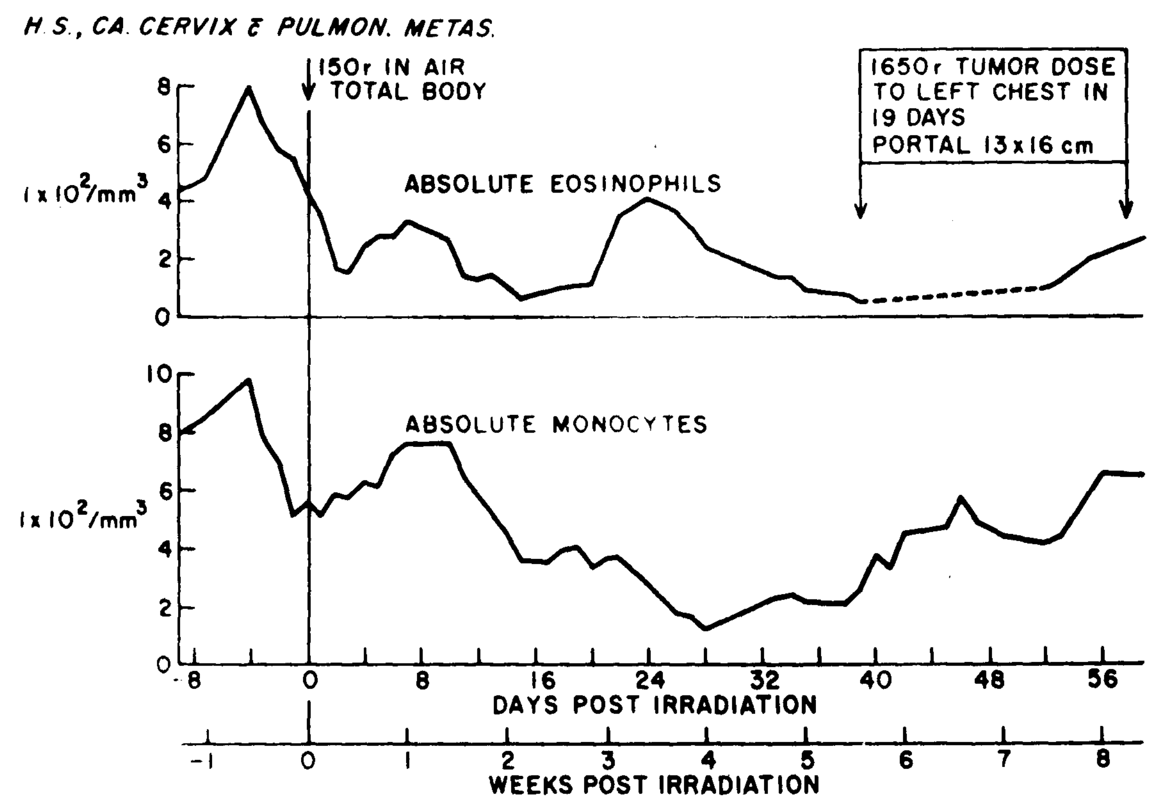
9



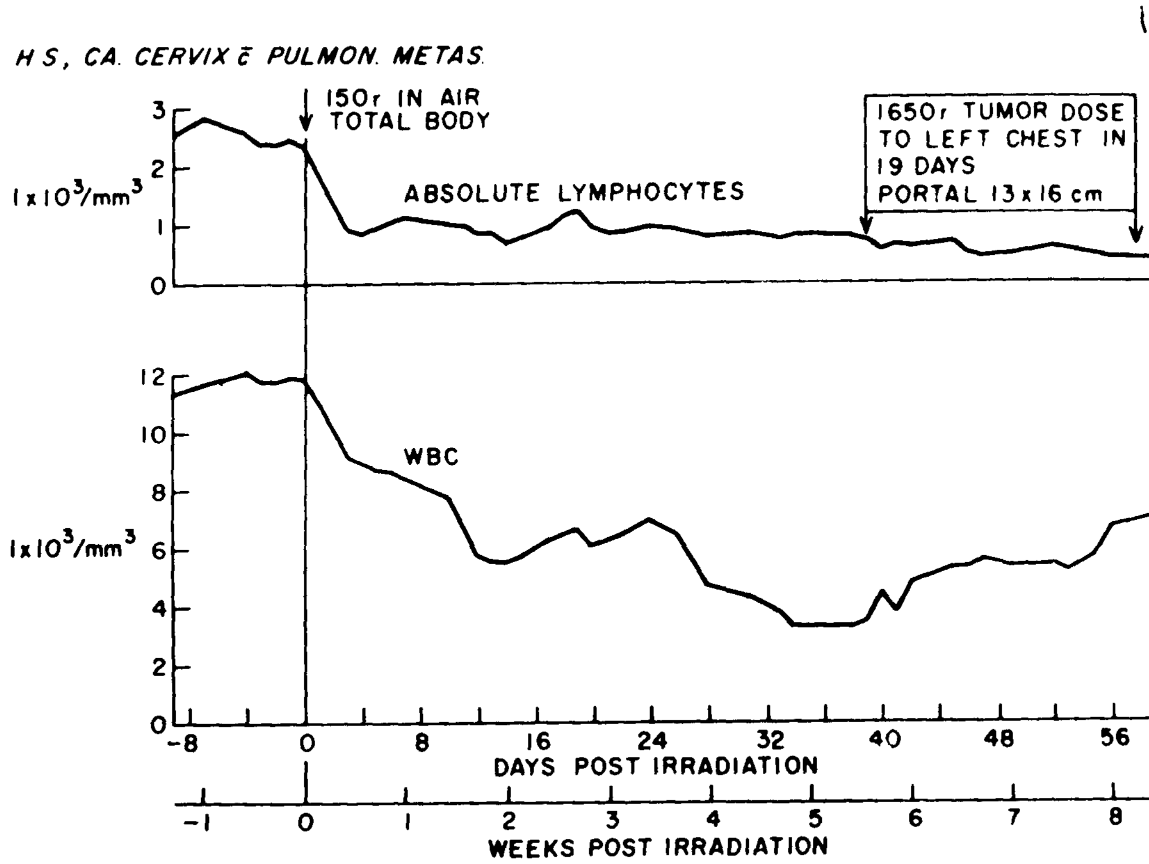

H.S., CA. CERVIX c̄ PULMON. METAS.
150r IN AIR TOTAL BODY
1650r TUMOR DOSE TO LEFT CHEST IN 19 DAYS PORTAL 13x16 cm
HEMOGLOBIN
250cc WB
500cc WA
gms %
15
13
11
9
RBC
1x10⁶/mm³
5
4
3
2
RECTIC
%
2
1
0
-8
0
8
16
24
32
DAYS POST IRRADIATION
-1
0
1
2
3
4
5
WEEKS POST IRRADIATION


H S, CA CERVIX c̄ PULMON. METAS.
150r IN AIR TOTAL BODY
1650r TUMOR DOSE TO LEFT CHEST IN 19 DAYS PORTAL 13x16 cm
PLATELETS
1x10⁵/mm³
4
3
2
1
0
ABSOLUTE GRANULOCYTES
1x10³/mm²
10
8
6
4
2
0
-8
0
8
16
24
32
DAYS POST IRRADIATION
-1
0
1
2
3
4
5
WEEKS POST IRRADIATION

12


H.S., CA. CERVIX c̄ PULMON. METAS.
150r IN AIR TOTAL BODY
1650r TUMOR DOSE TO LEFT CHEST IN 19 DAYS PORTAL 13x16 cm
ABSOLUTE EOSINOPHILS
1x10²/mm³
ABSOLUTE MONOCYTES
1x10²/mm³
DAYS POST IRRADIATION
WEEKS POST IRRADIATION

13


H.S., CA. CERVIX c̄ PULMON. METAS.
150r IN AIR TOTAL BODY
1650r TUMOR DOSE TO LEFT CHEST IN 19 DAYS PORTAL 13x16 cm
ABSOLUTE LYMPHOCYTES
1x10³/mm³
WBC
1x10³/mm³
DAYS POST IRRADIATION
WEEKS POST IRRADIATION

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