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ANNUAL REPORT

To

The Defense Atomic Support Agency

Contract No. DA-49-146-XZ-037

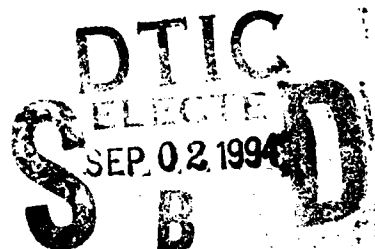
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THE STUDY OF THE POST-IRRADIATION SYNDROME IN MAN

Period of Report: January 1, 1960 - January 31, 1961

Date of Report: February 1, 1961



James J. Nickson, M.D.
Arvin S. Glicksman, M.D.

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Sloan-Kettering Institute for Cancer Research
Memorial-Sloan-Kettering Cancer Center
410 East 68th Street, New York 21, New York

94 8 26 156

Statement A
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SUMMARY

A report is made of the effects of total body irradiation in five patients and of head irradiation in twelve patients. Determinations were made of the formed elements of the blood, of plasma, and of the urinary excretion of creatine, creatinine, and pentose and of neurologic changes.

Of the five patients receiving total body irradiation from the 2 Mev van de Graaf generator, three received single exposures: one received 88 r; one, 50 r, and one, 50 r plus 4,000 r to the abdomen. Two patients received fractionated doses: one received 25 r for five consecutive days; the other received 25 r plus two sham irradiations at weekly intervals thereafter, and nine months later, 30 r x 3 at weekly intervals.

Hematologic changes remained the most consistent index of radiation exposure, showing variable decreases in lymphocyte counts and platelet counts post-irradiation. The profile score technique (Thoma and Wald) was adapted to compare post-irradiation values with the patient's own pre-irradiation values. It was found that 30 r x 3 produced a more severe depression of the hematologic system than comparable total dosage delivered at one exposure. Urinary excretion of creatine, creatinine, and pentose appeared to increase with increased radiation dosage.

Approximately one in three or one in four of the individuals receiving total body irradiation or whole head irradiation have shown significant EEG changes, most consistently seen four hours post-irradiation. These changes are transient, appear only in the EEG's taken when the patient was asleep, and are not associated with any clinical or conscious manifestations. Further study will be required to elucidate the significance of these observations.

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STUDY OF THE POST IRRADIATION SYNDROME IN MAN

The object of this investigation has been to study the post irradiation syndrome in humans in as many parameters as possible and to evaluate the effects of low doses of total body irradiation on modification of tumor response. The selection of patients and the dosage schedules were essentially the same as set forth perviously in our annual reports to the Department of the Army. The emphasis during the period of this report was on repeated small doses of irradiation. Six courses of total body irradiation were followed in five patients for periods of time from 40 to 80 days. Radiation was delivered with the 2 Mev van de Graaf generator. Three patients received single exposures: one received 88 r, one 50 r and a third patient received 50 r total body followed within the week by the onset of a course of irradiation to large portals on the abdomen. During the next 26 days this patient was given a midplane dose of 4000 r. Two patients received fractionated doses of irradiation: one received 25 r for five consecutive days; the second patient received 25 r and received two sham irradiations at weekly intervals thereafter. Nine months later this patient returned and received 30 r x 3 at weekly intervals.

HEMATOLOGIC DATA*

While the hematologic data has remained the most consistent index of radiation exposure, individual variation for each of the formed elements has been noted in one patient or another. Twenty-five r

* See accompanying charts

produced a fall in the lymphocyte count during the first week post-irradiation in one patient while 50 r produced very little change in the absolute lymphocyte count in another patient. Twenty-five r produced a very transient drop in the platelet count, the lowest point being observed on the 28th day. On the other hand, 50 r resulted in a very gradual fall in platelet count which, however, never fell below 100,000 during the 56 days post-irradiation.

It was observed in one patient that 88 r total body irradiation produced a depression in the platelet count during the fourth to fifth week post-irradiation. On the other hand, 30 r x 3 produced a marked fall in the platelet count that started essentially at the same time but remained depressed until the 60th day post-irradiation.

In an attempt to compare the biological response to these measured doses of irradiation, the profile score technique originally suggested by Thoma and Wald (G.E. Thoma, Jr., N. Wald. J. of Occup. Med. 1:421 August 1959) has been employed. However, in our patients, the pre-irradiation baseline values were utilized rather than the universal means employed by these authors. It was felt that the patient's own baseline would more significantly reflect changes produced by exposure to the total body irradiation. Twenty-five r and 50 r produced cumulative profile scores which were very low, in the range of 10 to 15. Eighty-eight r produced an accumulative score of approximately 75 to 85. Significantly, 30 r x 3 produced an accumulative profile score of over 200 and 25 r x 5 produced an accumulative score of 175. The patient who received 50 r total body irradiation followed by 4000 r abdominal irradiation accumulated

a profile score of almost 400. Thus it would appear that as far as the hematologic system is concerned, 30 r x 3 has a more severe depressive effect than a comparable dosage delivered at one exposure. This observation will require further documentation. Because the profile appears to be a useful method of comparing the integrated biological response of sensitive tissues to total body irradiation, we are currently analyzing the data accumulated during the last five years in a similar manner and will report the results at a future date.

PLASMA, PROTEIN AND ELECTROPHORESIS*

Serial examination of plasma has as yet failed to reveal any specific pattern associated with the post-irradiation syndrome at the level of irradiation in these patients. It is interesting to note that transient changes occurring in the first 24 hours post-irradiation were also seen in the patient who received sham irradiation. At this time we are inclined to believe that these changes may be associated with apprehension and stress rather than a direct consequence of the exposure to ionizing irradiation.

URINE EXCRETION DATA*

The determination of the urinary excretion of creatine, and expressed as per cent creatine of daily urinary creatine and creatinine excretion, continued during the last year. In the patient who received 25 r total body irradiation followed by sham irradiation during the next two periods, there was no significant increase in creatine excretion.

* See accompanying charts

In the patient who received 88 r total body irradiation, significant increase in creatine excretion was noted between the fourth and fifth weeks post irradiation. The creatine excretion in the patient with multiple myeloma was transiently increased between the second and third week. However, the significance of the data after this time is in doubt since the patient developed increasing evidence of renal impairment, ultimately developing oliguria and anuria on the 35th day post-irradiation. It is interesting to note that the highest per cent creatine found by our laboratory was in the patient who received 50 r total body followed by 4000 r to the total abdomen for treatment of carcinoma of the colon. In this patient there was a phenomenal excretion of creatine during the entire period of observation.

Urinary excretion of pentose increased in every patient receiving total body irradiation. There was a small increase in excretion of pentose between the first and second week post-irradiation in the patient who received 25 r total body irradiation. The sham irradiations were not followed by a similar increase in pentose. Eighty-eight r total body irradiation produced a significant increase in pentose excretion between the third and fourth weeks post-irradiation. In the patient with multiple myeloma who received 25 r x 5, there was a transient increase in pentose excretion between the first and second week. However, since he showed signs of progressive renal failure between the fourth and fifth weeks, the data at this time is not felt to be significant. There was significant

increase in pentose excretion in the patient who received 50 r total body irradiation followed by abdominal baths. In this patient there was a two and a half fold increase in pentose excretion in the fourth to fifth weeks.

Creatinuria following irradiation has been consistently reported in animals at a much higher order of magnitude but not in man at such low levels of irradiation. The significance of the pentose excretion may be related to cell destruction in the release of nuclear material. On the other hand, it may be related to a specific enzymatic abnormality in the pentose monophosphate shunt causing a blockade and thereby an excess which then clears the renal threshold.

ELECTROENCEPHALOGRAPH STUDIES*

To study the possibility that small amounts of irradiation may produce objectively measurable changes in brain function, patients receiving total body irradiation have been followed closely with electroencephalographic tracings. Twelve patients have been studied in the last year (see Table 1). The first group of patients received total body irradiation. One patient who had normal pre-irradiation EEG's developed a transient seizure pattern 4 hours post irradiation. This abnormality was seen on the record taken while asleep but not while awake. All remaining 70 EEG's taken during the entire post-irradiation period of observation of 50 days were normal. Two patients received

* See accompanying charts

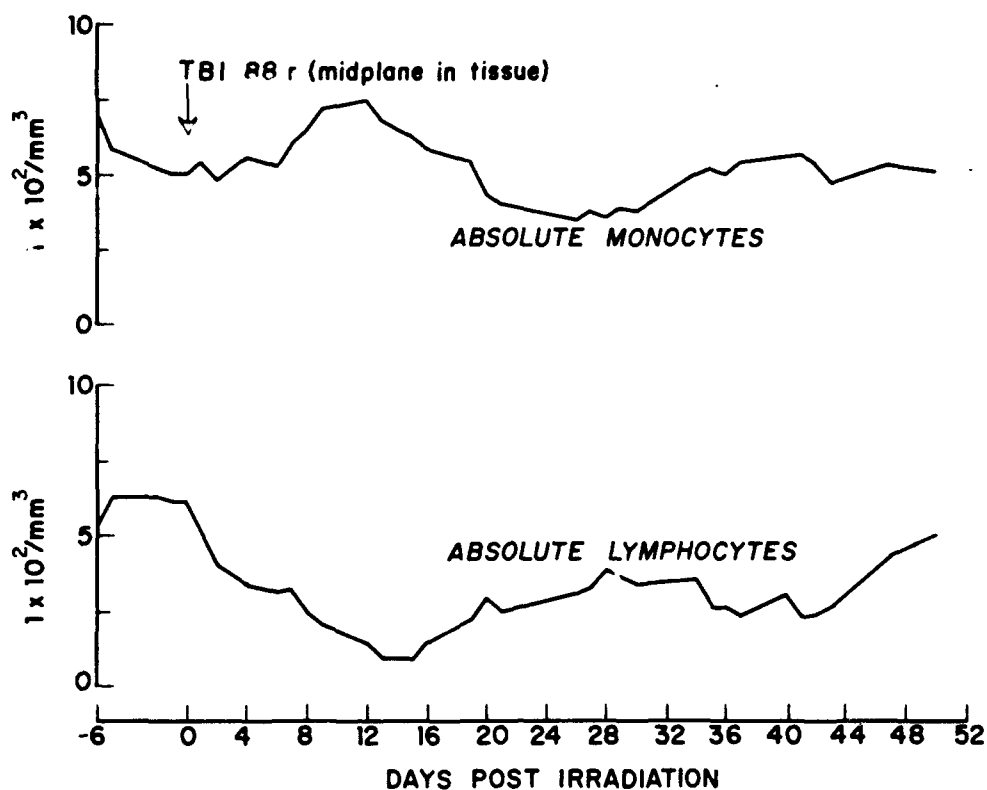
irradiation to the head utilizing the identical radiation setup as was used in the total body irradiation. In one patient, spike waves and an abnormal pattern during sleep developed 4 hours after irradiation. In one of the three patients with brain metastases from breast carcinoma who were receiving total head irradiation, transient decomposition of the already pathologic patterns was discernible following each radiation exposure. It was felt that these changes represented abnormalities produced by the x-irradiation. Two patients received irradiation to the head utilizing the electron beam of the Betatron. In one, the electrons had an energy of 10.4 Mev which gave an isodose distribution throughout the scalp, skull and only the outer 1 cm of cerebral cortex. In this patient no irradiation effect was seen. In another patient where 22.5 Mev electron beam was utilized so that a homogeneous irradiation of the entire brain occurred, there was consistent effect four hours after each radiation exposure. As a control, a patient with a hepatoma who was receiving radiotherapy to the liver was followed by daily EEG's. Essentially the same volume of tissue was irradiated as when the entire head is irradiated. The dose delivered to the midplane of the liver was essentially the same as the dose to the midplane of the brain in patients receiving total head irradiation, i.e., 3000 r. In this patient, normal pre-irradiation EEG's changed to questionable pathologic patterns four and twelve hours post-irradiation which may have some relation to the x-irradiation. These abnormalities were seen in only two records on this patient. The remaining 25 records were absolutely normal.

Two electroencephalographists have read the electroencephalograms independently and without knowledge of each other's findings. In a few instances, there has been disagreement in the interpretation of the records. These records were then resubmitted to the electroencephalographists for further consideration. When the differences could not be resolved, the records have been put aside to be read by a third independent electroencephalographist.

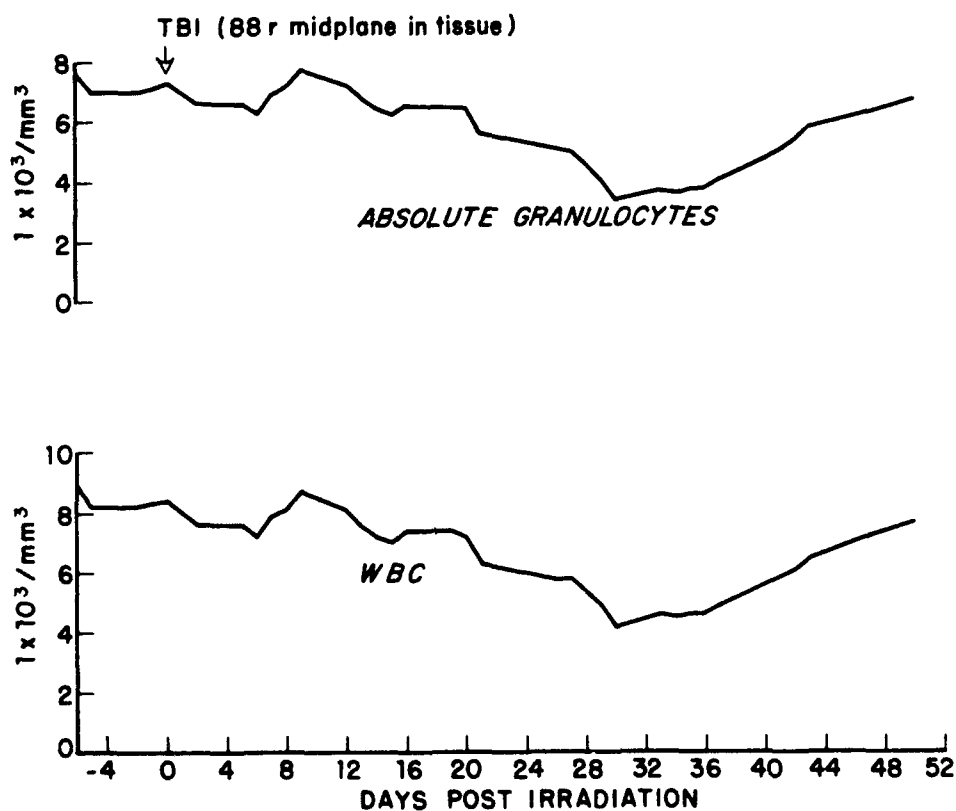
At this time it would appear that approximately one in three or one in four of the individuals receiving total body irradiation or whole head irradiation have shown significant EEG changes which were most consistently seen four hours post-irradiation. These changes are transient, not associated with any clinical or conscious manifestations on the part of the patients. Only the records taken while the patients are asleep have shown any change; those taken while they were awake have been normal. Therefore, there is a strong possibility that these changes relate to abnormality in thalamic function resulting from the total body exposure. It is appreciated that these are preliminary observations, the significance of which will have to be determined by further study.

Pt.	Age	Sex	Diagnosis	Irradiation			Pre Irradiation	4 hrs. post Irradiation	8 & 12 hrs. Post-irrad.	Comment
				Area	Energy	Dose in Tissue				
L.R.	47	M	Melanoma	TBI	2 Mev	88r	Normal	Seizure pattern on sleep record	Normal	only 4 hr. record abnormal most likely radiation effect
L.D.	57	F	Ca. Cervix	TBI	2 Mev	50r	Normal	Pathologic during sleep record	Normal	Probable radiation effect seen in 4 hr. record
R.F.	31	F	Mycosis Fungoides	TBI	2 Mev	25r + 2 shams at weekly intervals	Probably pathologic	Probably pathologic	Probably pathologic	No specific effect denoted
H.F.	31	F	Mycosis Fungoides	TBI	2 Mev	30r x3 at weekly intervals	Probably pathologic	Questionable seizure pattern	Probably pathologic	Questionable radiation effect
T.K.	60	F	Ca. breast skull & scalp met.	Head	Electron beam	200r/d	Pathologic	Pathologic	Pathologic	No radiation effect seen, only scalp, skull & 1 cm of context irradiated
A.B.	44	F	Ca. breast	Head	Electron beam	100r/d	Normal	Pathologic after each treatment	Normal	Consistent effect most likely due to irradiation
W.D.	62	M	Ca. floor of mouth	Head only	2 Mev	100r	Normal	Spike waves - abnormal pattern during sleep	Normal	Pathologic pattern most likely due to radiation exposure setup identical to TBI
E.G.	43	M	Ca. esophagus	Head only	2 Mev	30r x 3	Normal	Normal	Normal	No specific effect noted exposure setup identical to TBI
E.S.	61	F	Ca. breast brain met.	Head	250 kv	150r/d	Pathologic	Pathologic	Pathologic	No specific effect of radiation noted
A.C.	63	F	Ca. breast brain met.	Head	250 kv	150r/d	Pathologic	Pathologic	Pathologic	No specific effect noted
M.M.	48	F	Ca. breast brain met.	Head	250 kv	150r/d	Pathologic	Decomposition of usual pattern	Pathologic	Transient worsening of abnormalities after each radiation exposure
S.M.	19	F	Hepatoma	Liver	Co60	175r/d	Normal	Possibly pathologic	Possibly pathologic	Doubtful, if any, effect due to radiation

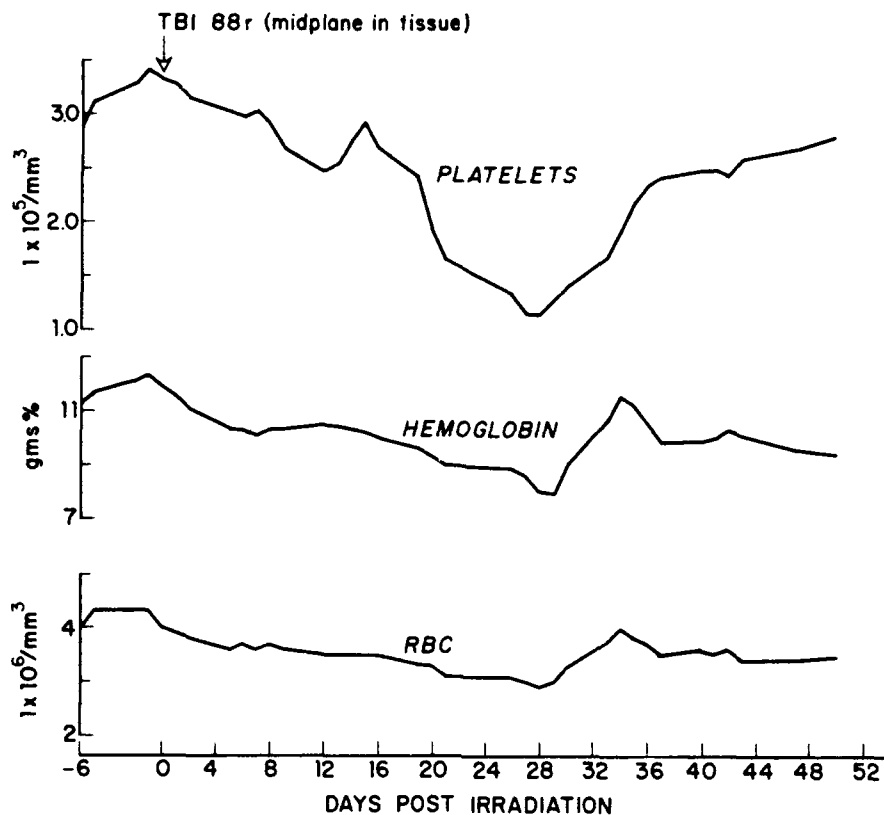
L.R., 47yrs. ♂, MELANOMA



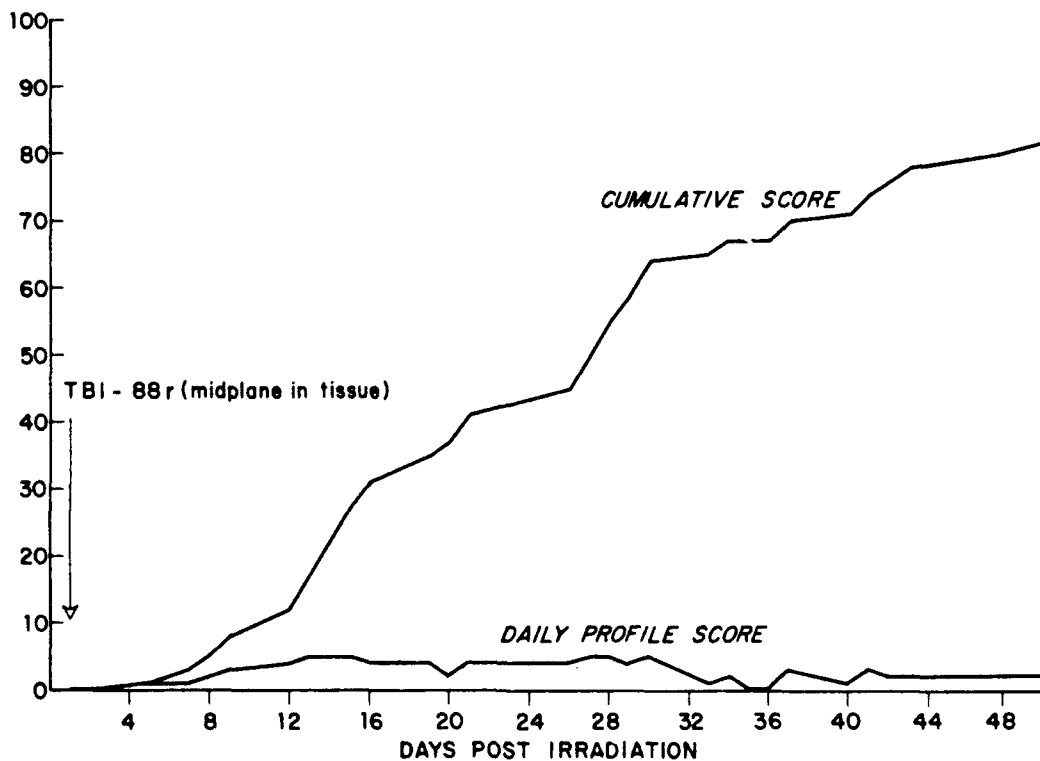
L.R., 47yrs. ♂, MELANOMA



L.R., 47yrs. ♂, MELANOMA



L.R., 47yrs ♂, MELANOMA



TBI 88r (midplane in tissue)

Total Protein

Alb.

Globulin

α_1

α_2

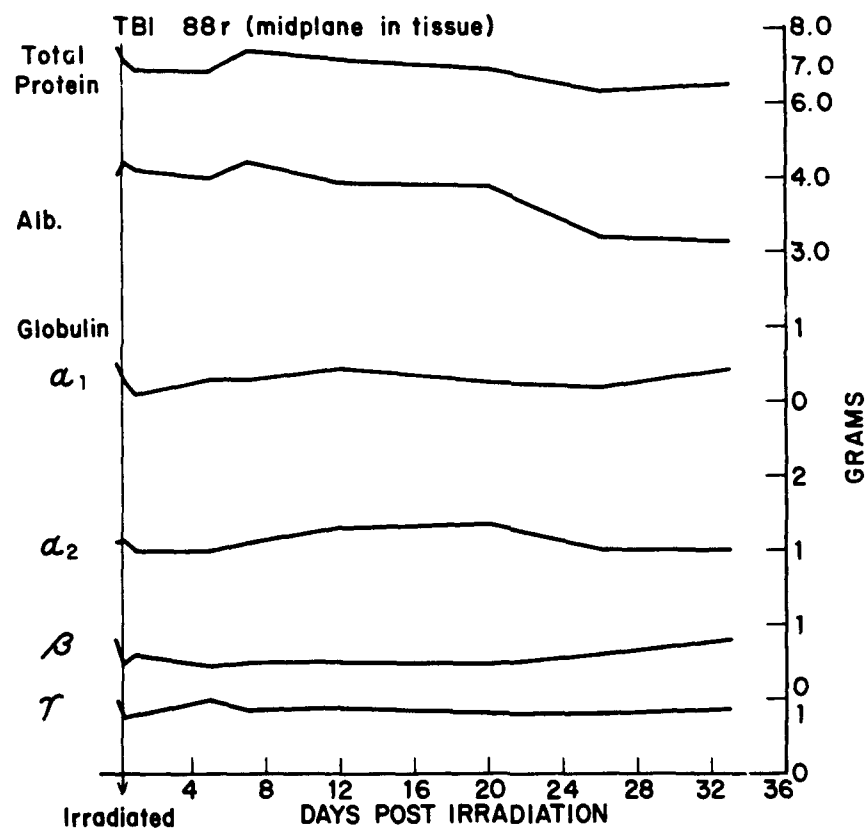
β

γ

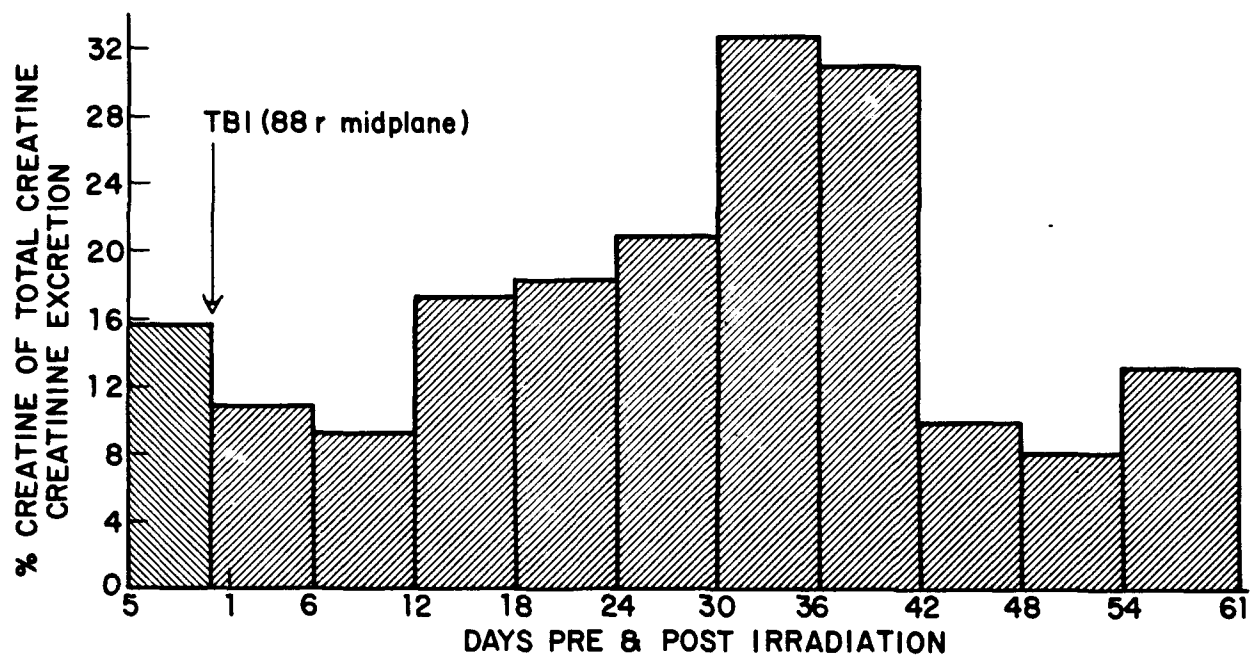
GRAMS

IRRADIATED

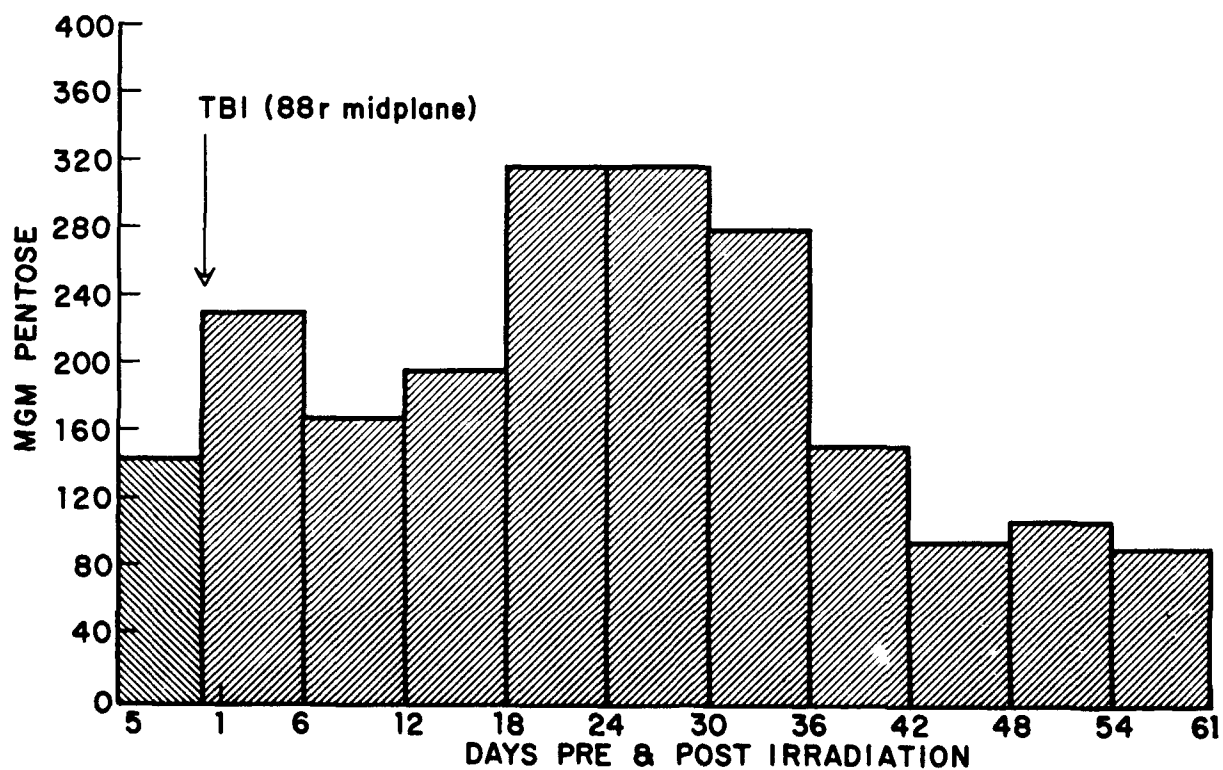
DAYS POST IRRADIATION



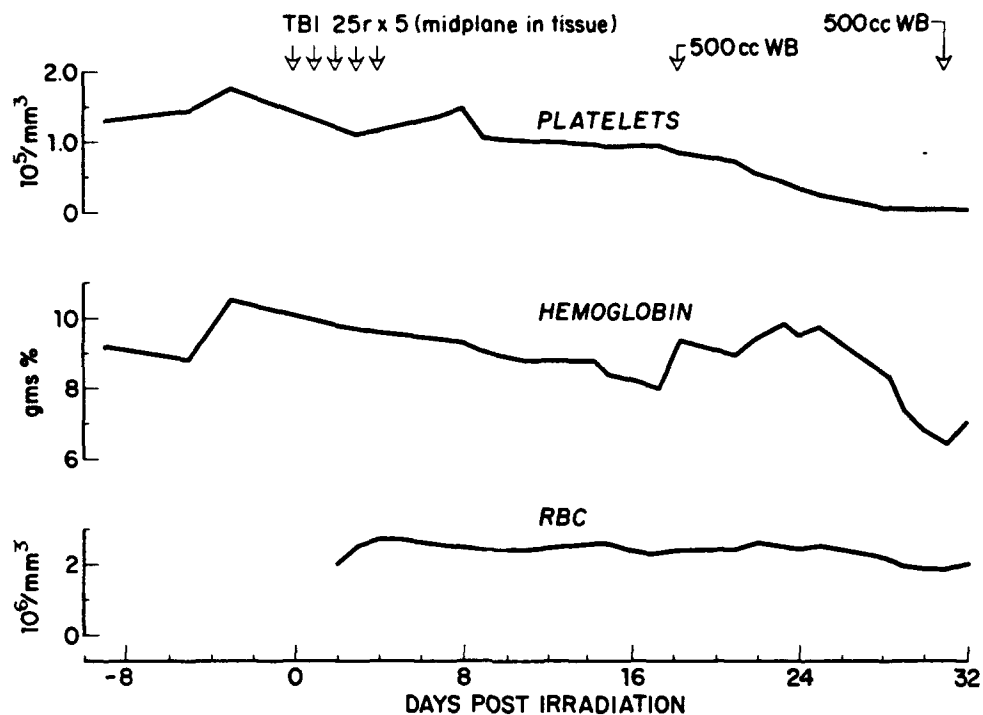
L.R., 47 yrs ♂, MELANOMA, CREATINE / CREATININE EXCRETION RATIOS



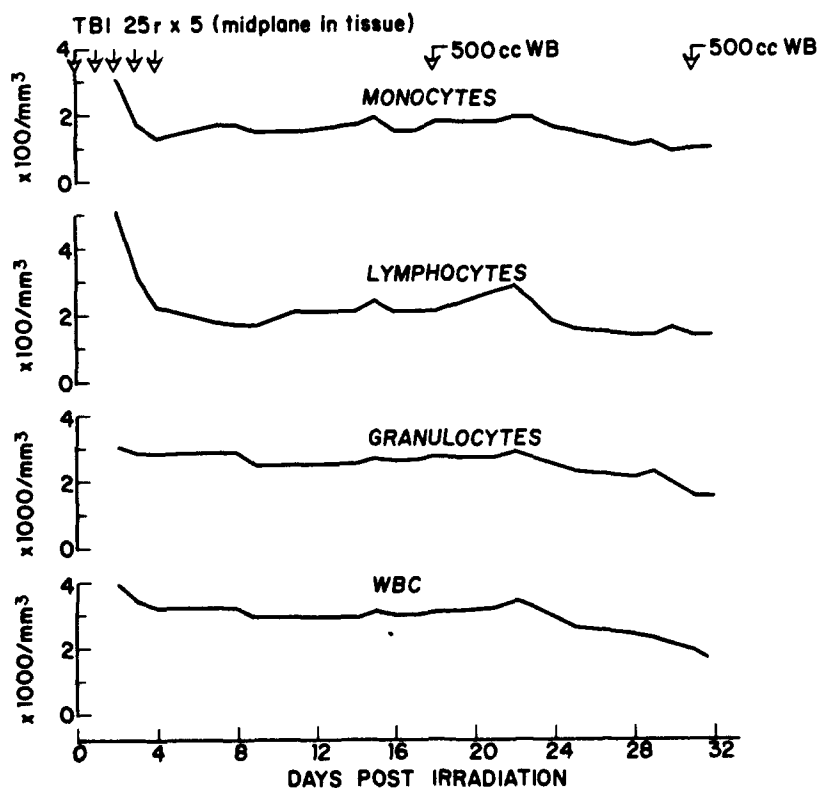
L.R., 47 yrs ♂, MELANOMA, URINARY EXCRETION, PENTOSE



J.C., 62yrs, ♂, MULTIPLE MYELOMA

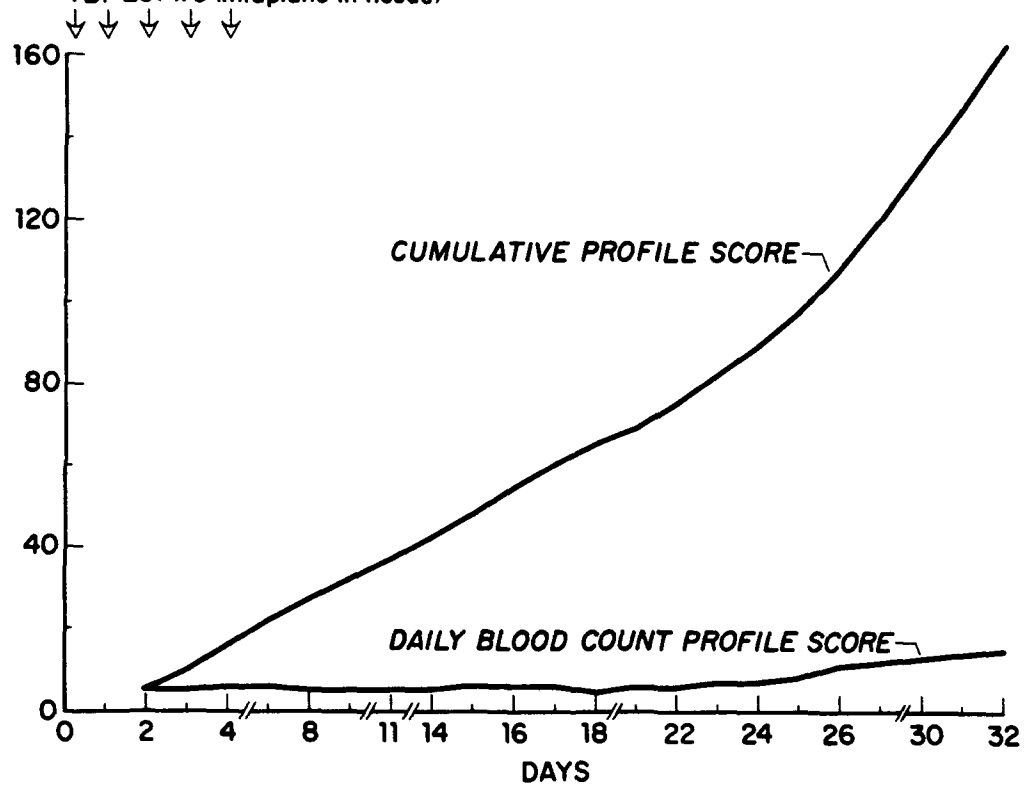


J.C., 62yrs, ♂, MULTIPLE MYELOMA



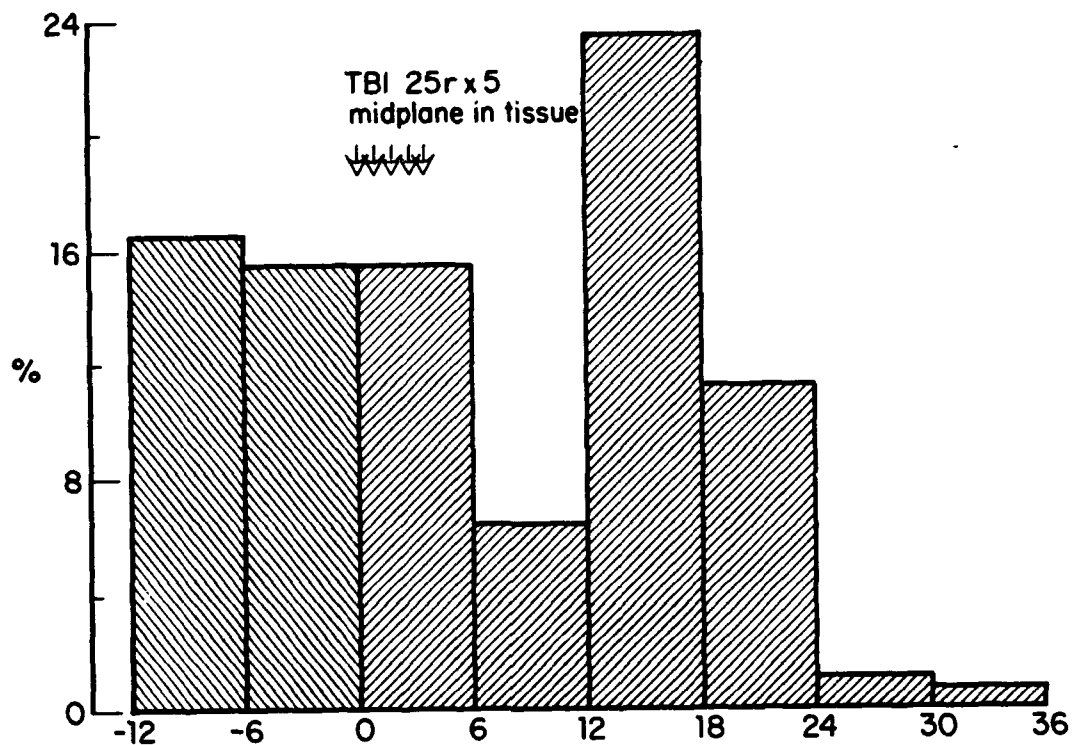
J.C., 62yrs, ♂, MULTIPLE MYELOMA

TBI 25r x 5 (midplane in tissue)



J.C., 62yrs, ♂, MULTIPLE MYELOMA

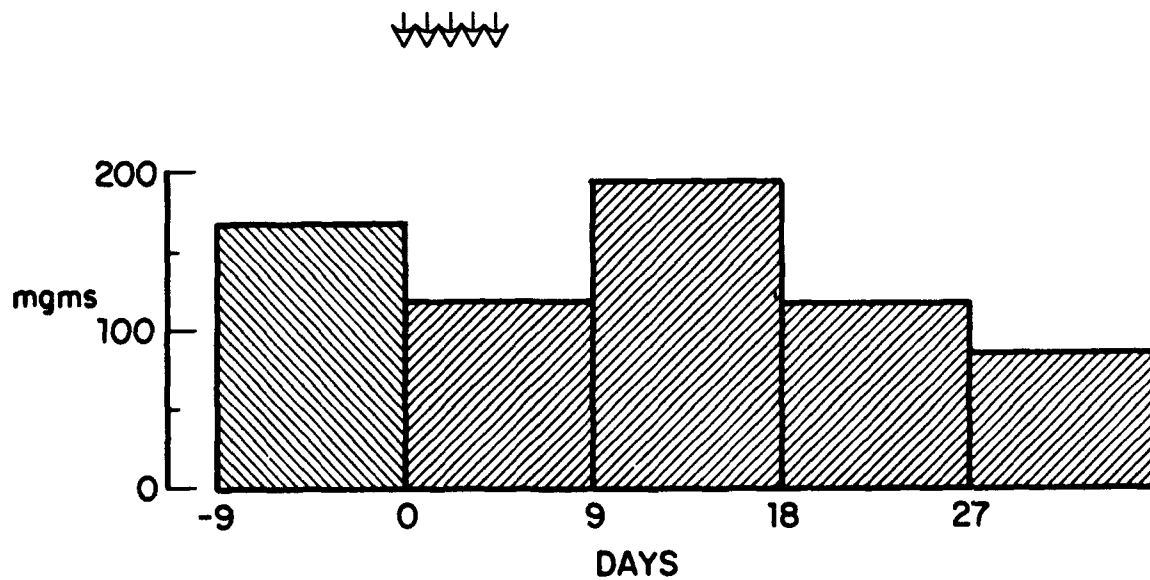
PER CENT CREATINE OF TOTAL DAILY URINARY CREATINE PLUS CREATININE



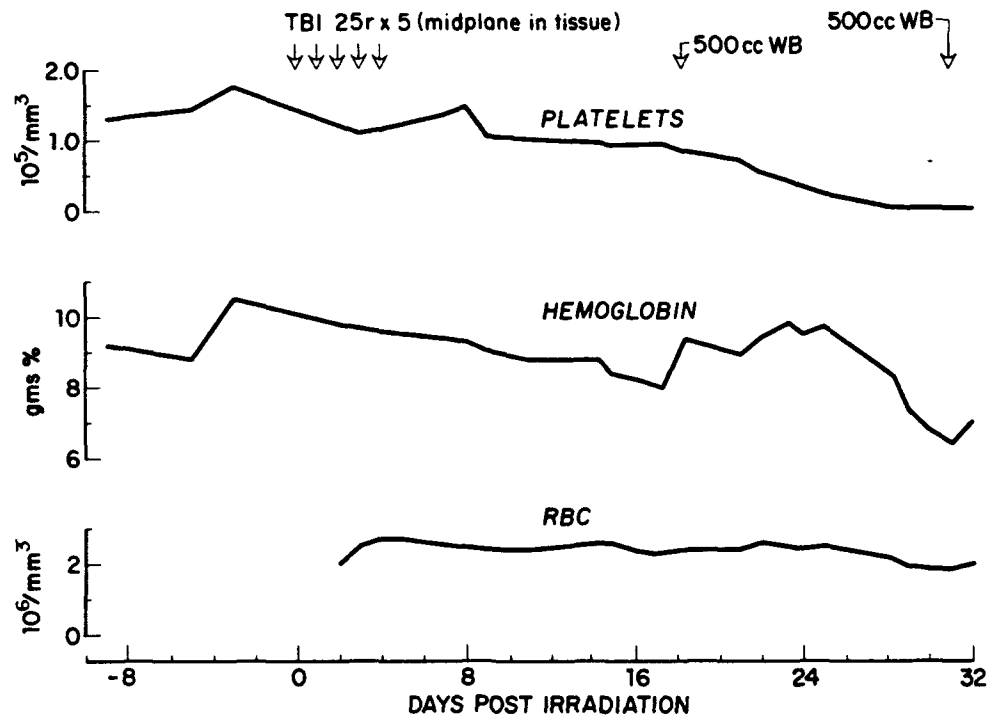
AVERAGE DAILY URINARY PENTOSE EXCRETION (MGM)

J.C., 62yrs, ♂, MULTIPLE MYELOMA

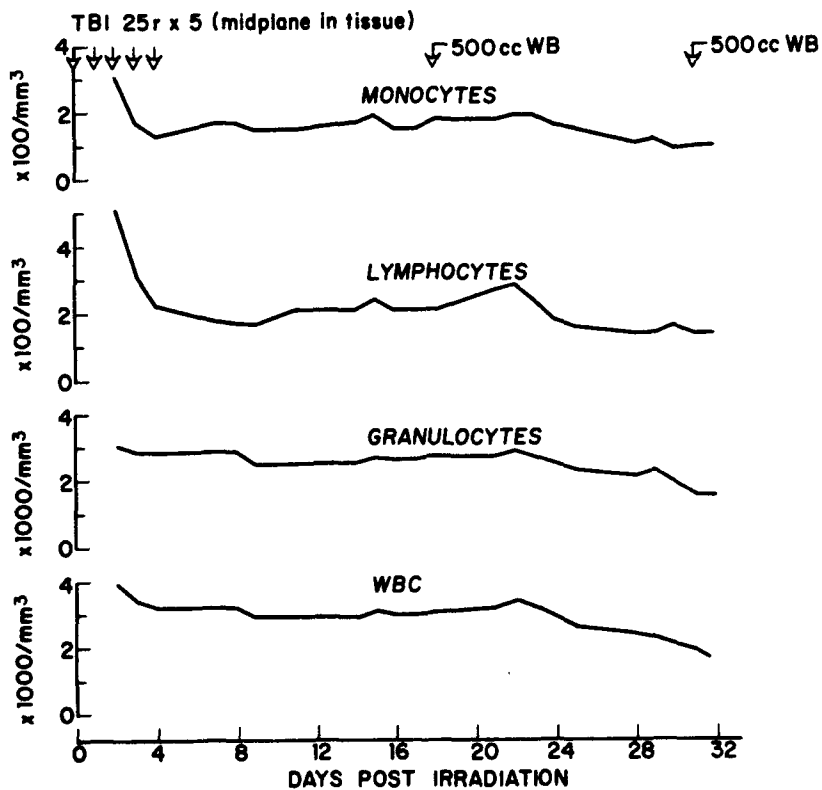
TBI 25rx 5 (midplane in tissue)



J.C., 62yrs, ♂, MULTIPLE MYELOMA



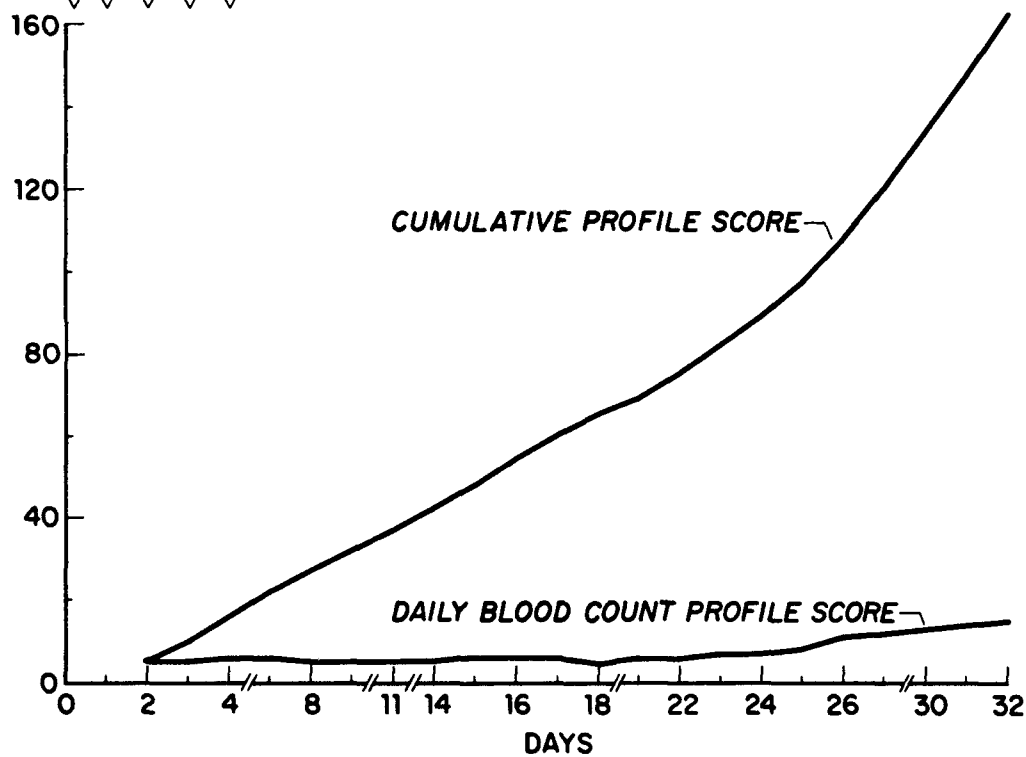
J.C., 62yrs, ♂, MULTIPLE MYELOMA



J.C., 62yrs, O, MULTIPLE MYELOMA

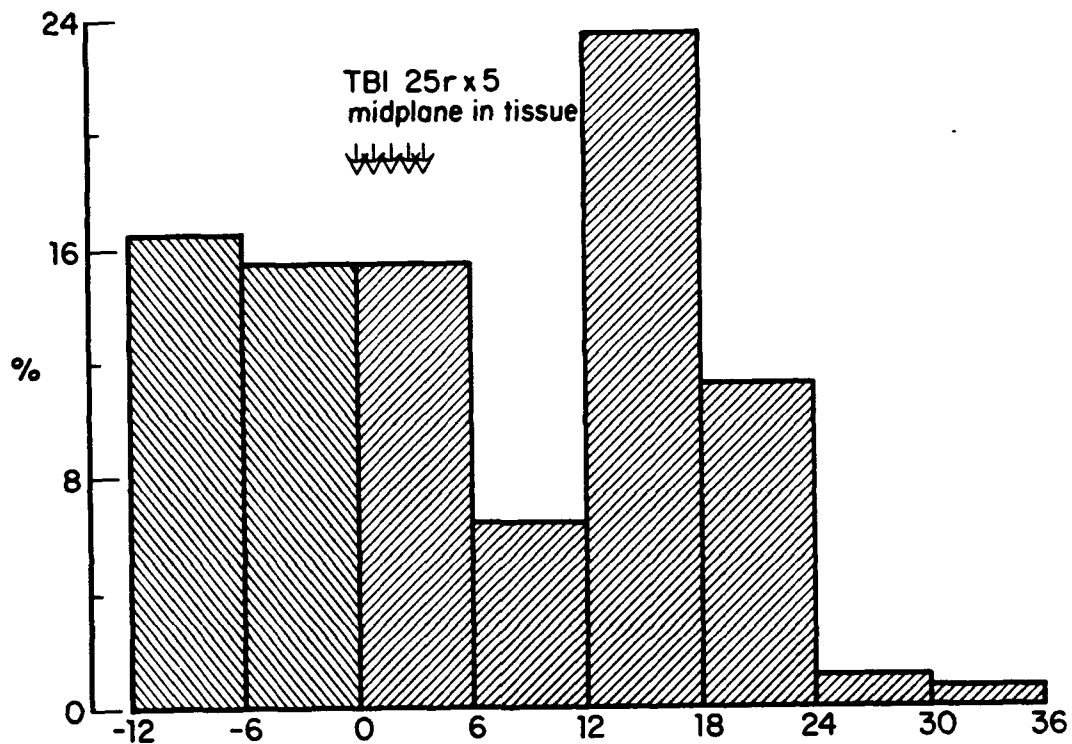
TBI 25r x 5 (midplane in tissue)

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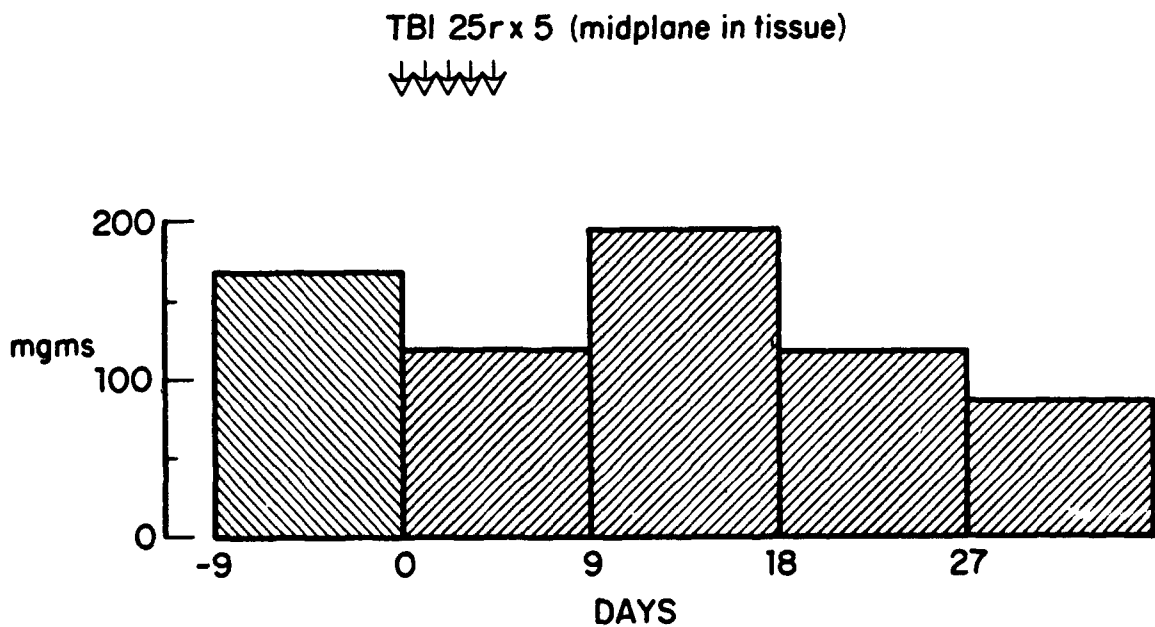


J.C., 62yrs, ♂, MULTIPLE MYELOMA

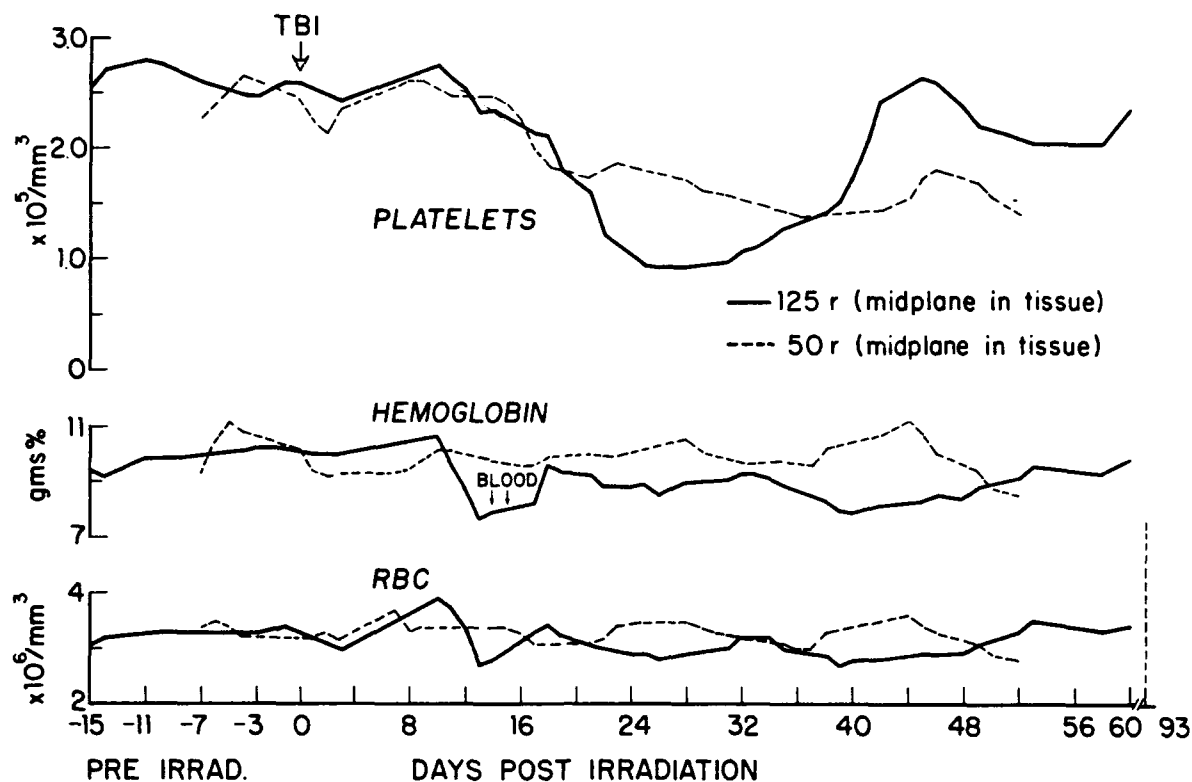
PER CENT CREATINE OF TOTAL DAILY URINARY CREATINE PLUS
CREATININE



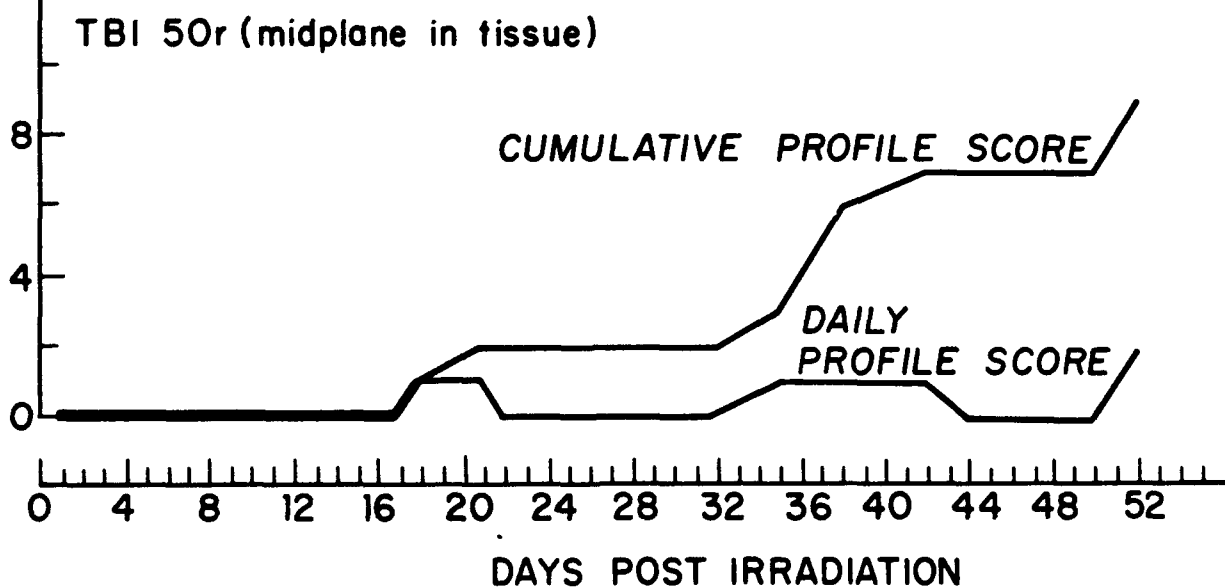
AVERAGE DAILY URINARY PENTOSE EXCRETION (MGM)
J.C., 62yrs, ♂, MULTIPLE MYELOMA



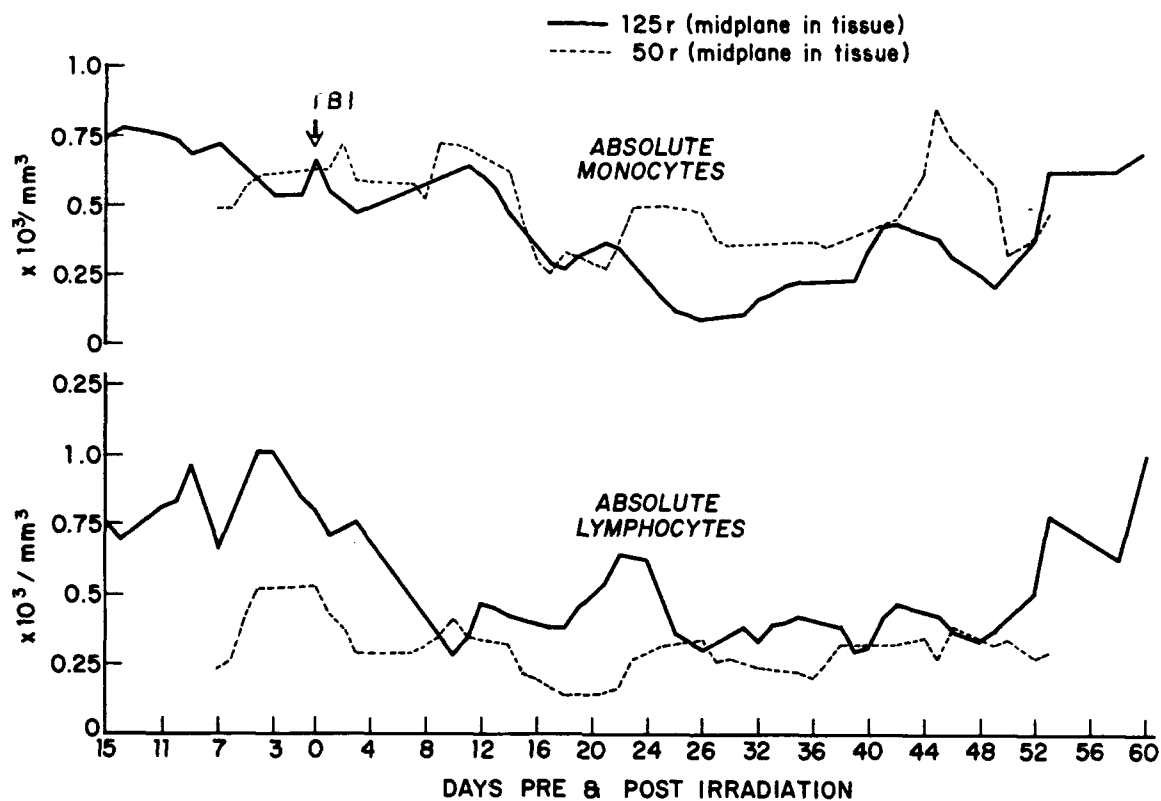
L.D. 57yrs., ♀, CA OF CERVIX



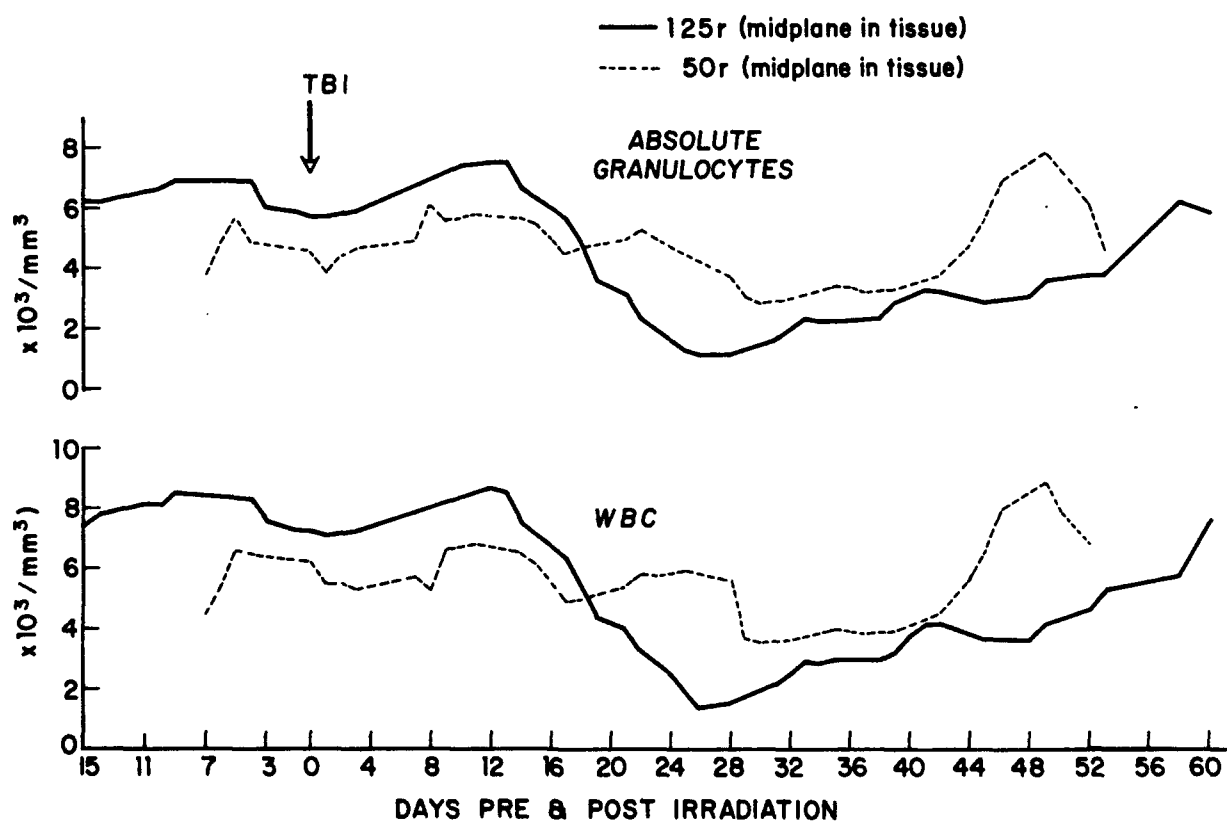
L.D., 57yrs., ♀, CANCER OF CERVIX



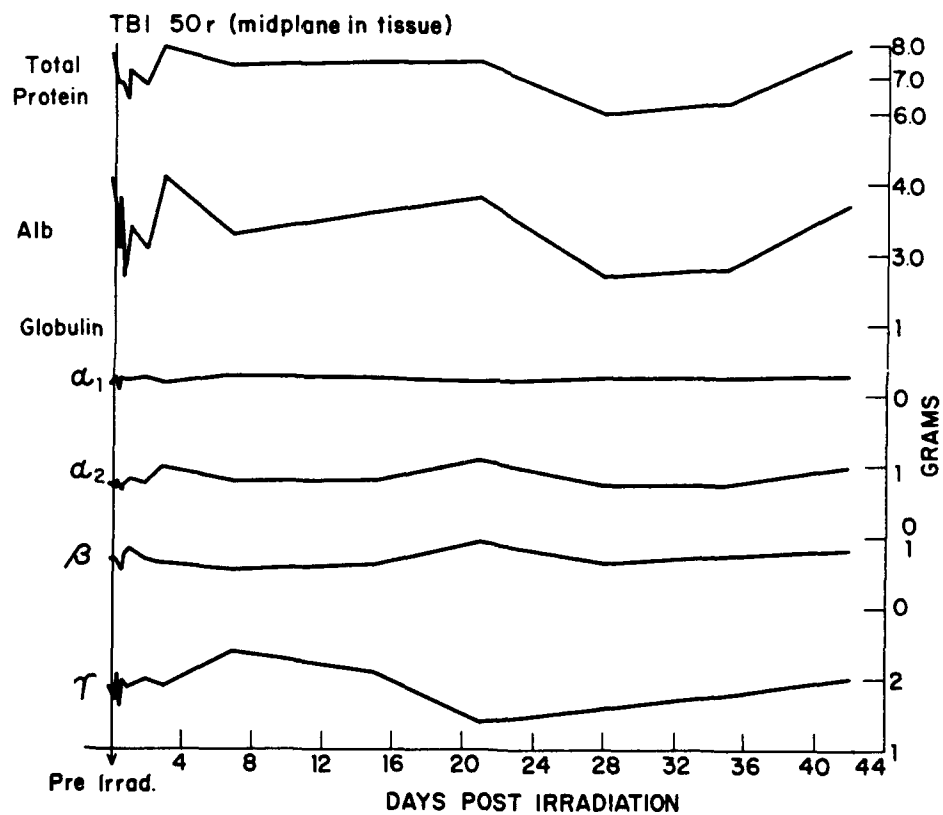
L.D., 57yrs ♀, CA OF CERVIX



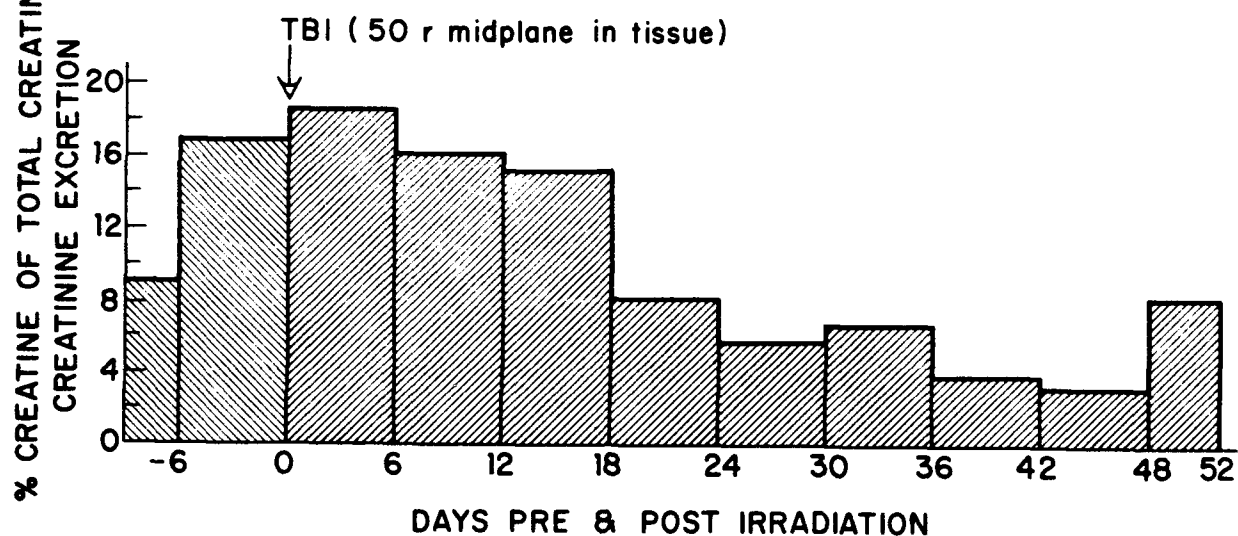
⁴ L.D., 57yrs ♀, CA OF CERVIX



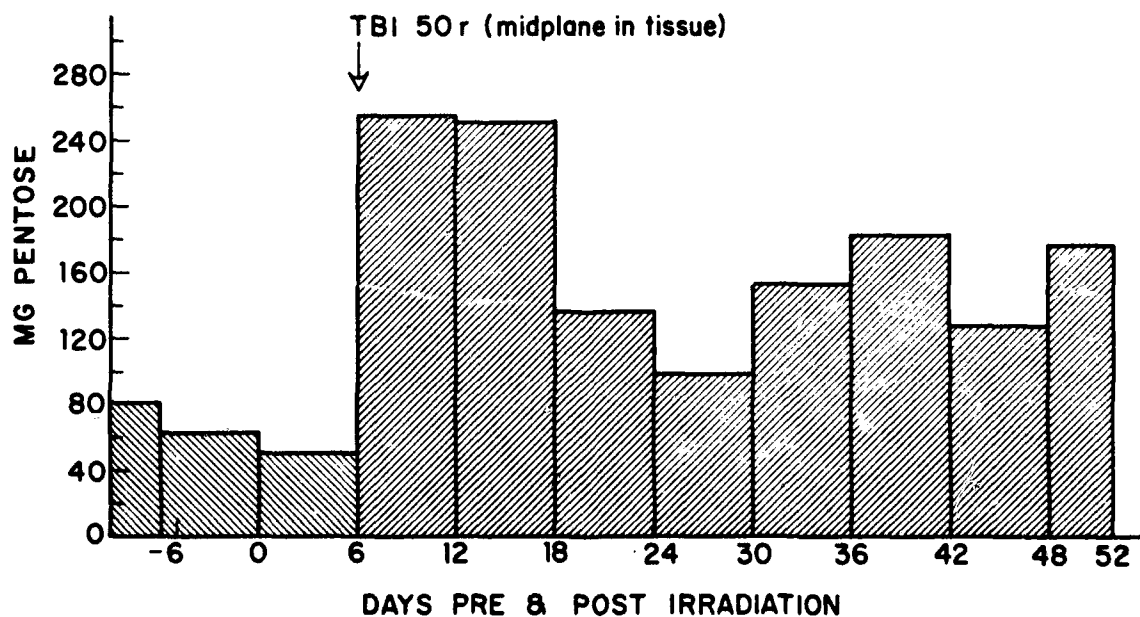
L.D., 57 yrs ♀ CA CERVIX, PLASMA PROTEIN ELECTROPHORESIS



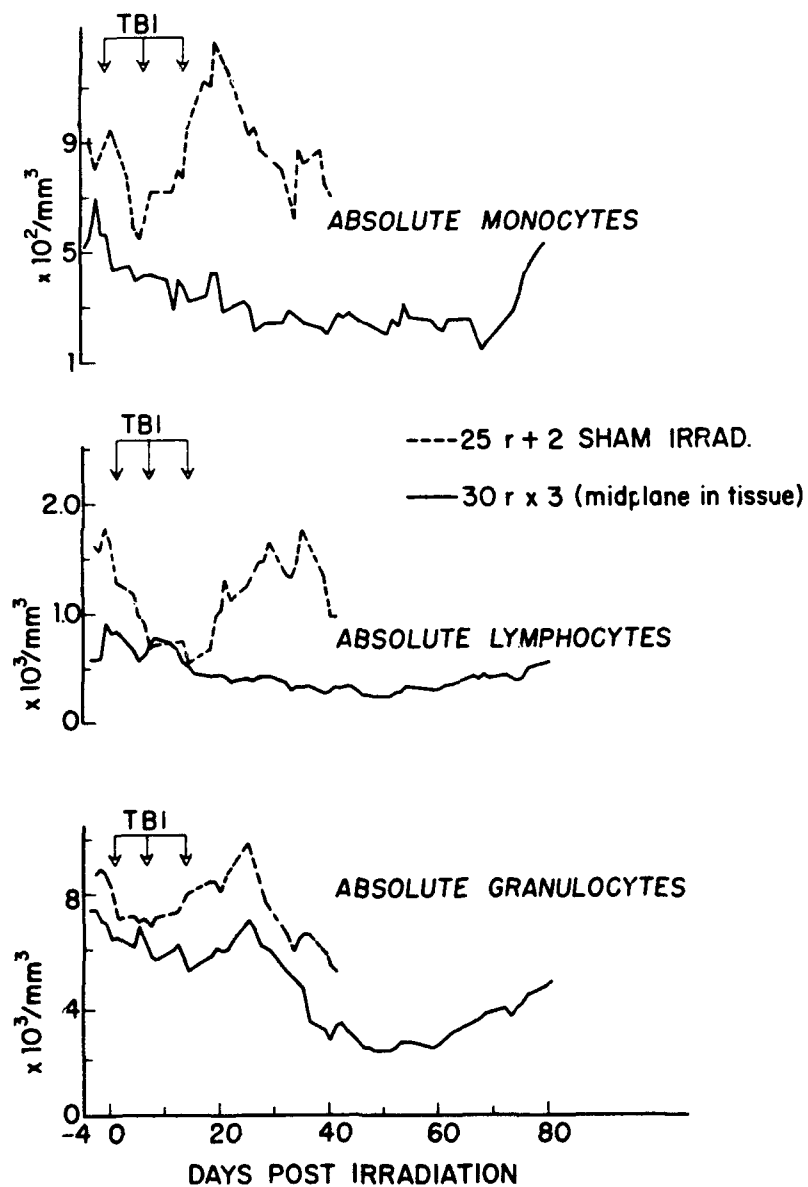
*L.D., 57 yrs. ♀, CA CERVIX, PERCENT CREATINE, TOTAL
DAILY URINARY CREATINE + CREATININE*



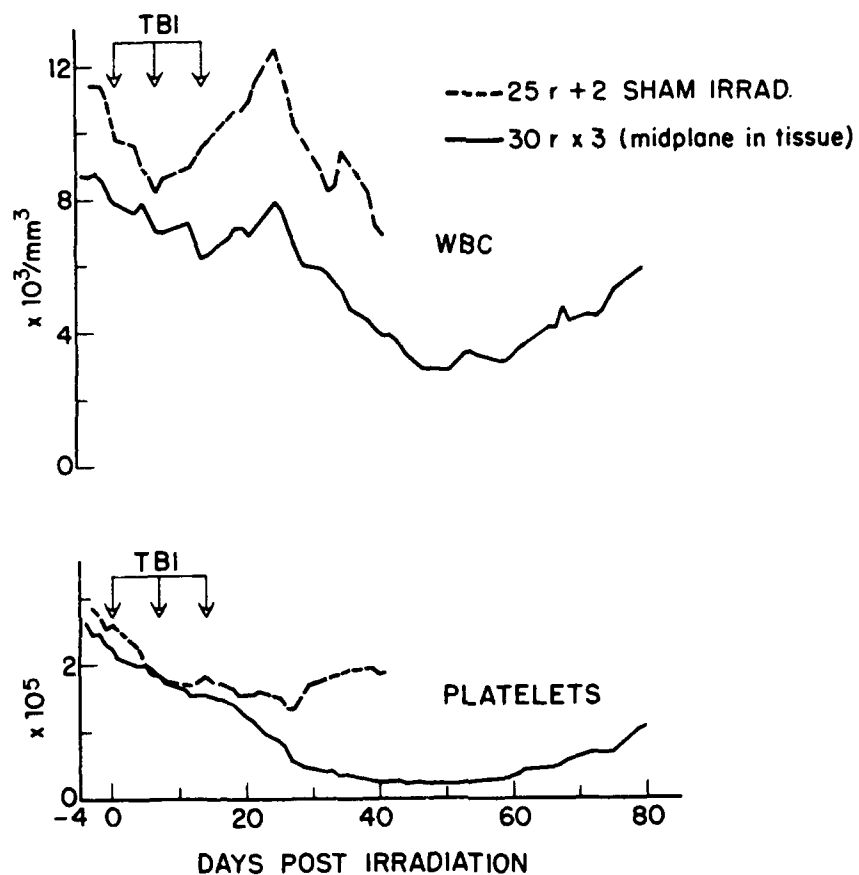
L.D., 57 yrs. ♀, CA CERVIX, AVERAGE DAILY URINARY PENTOSE EXCRETION



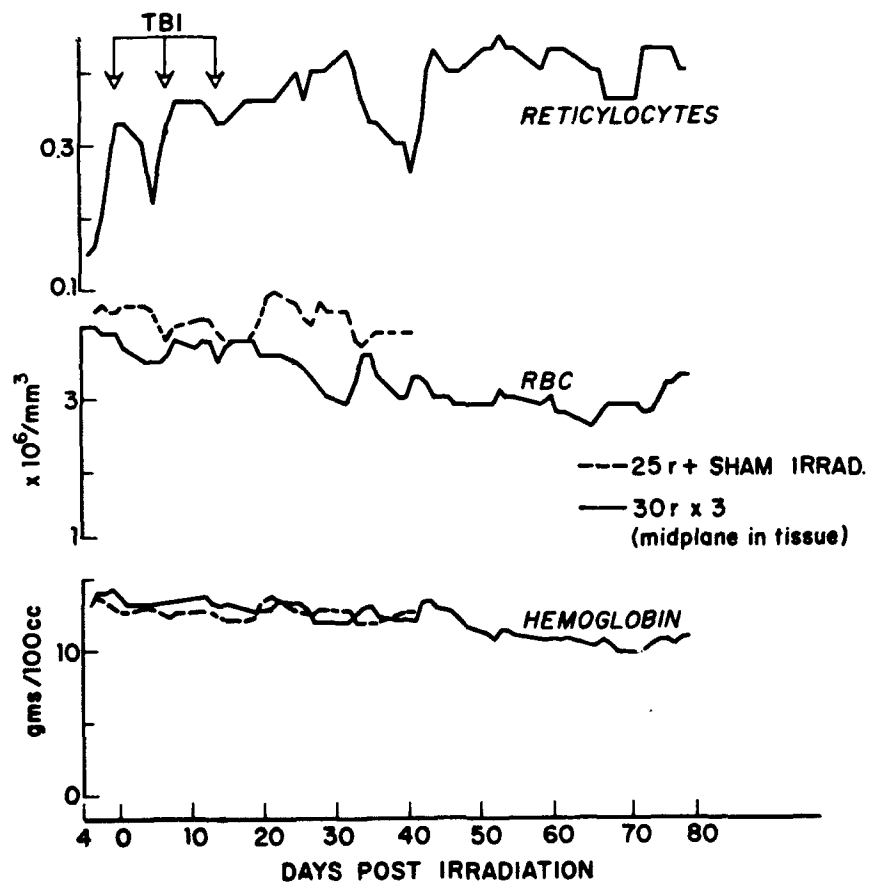
R.F. 30 yrs. ♀. MYCOSES FUNGOIDES



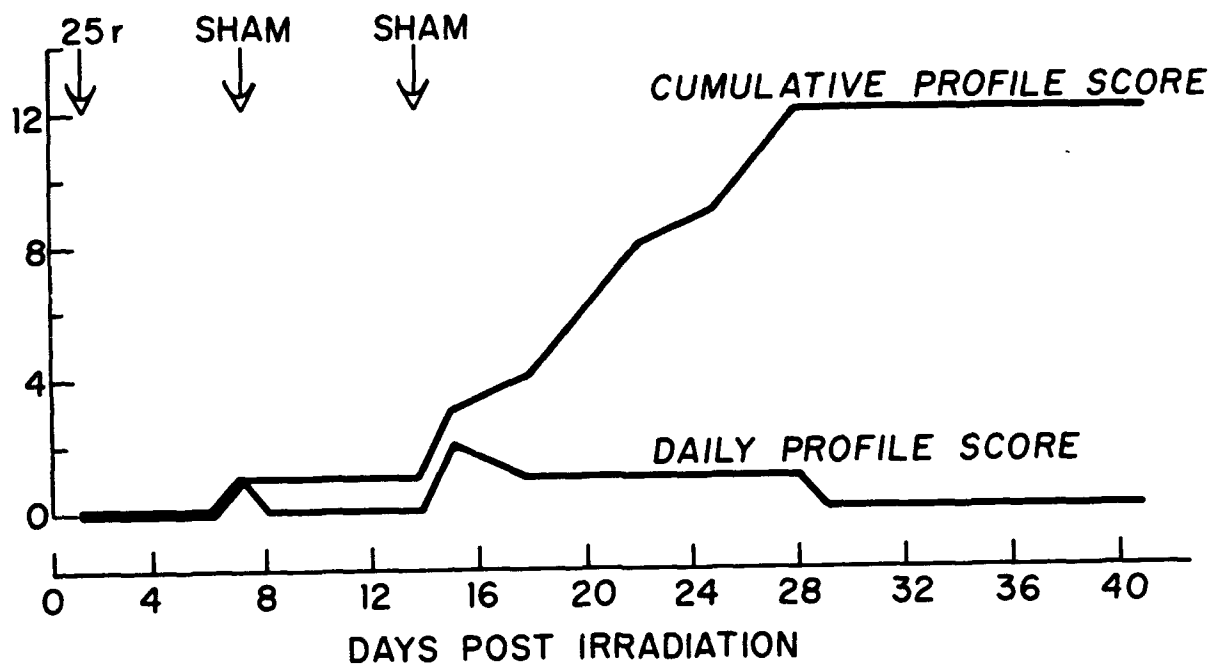
R.F. 30yrs. ♀, MYCOSES FUNGOIDES



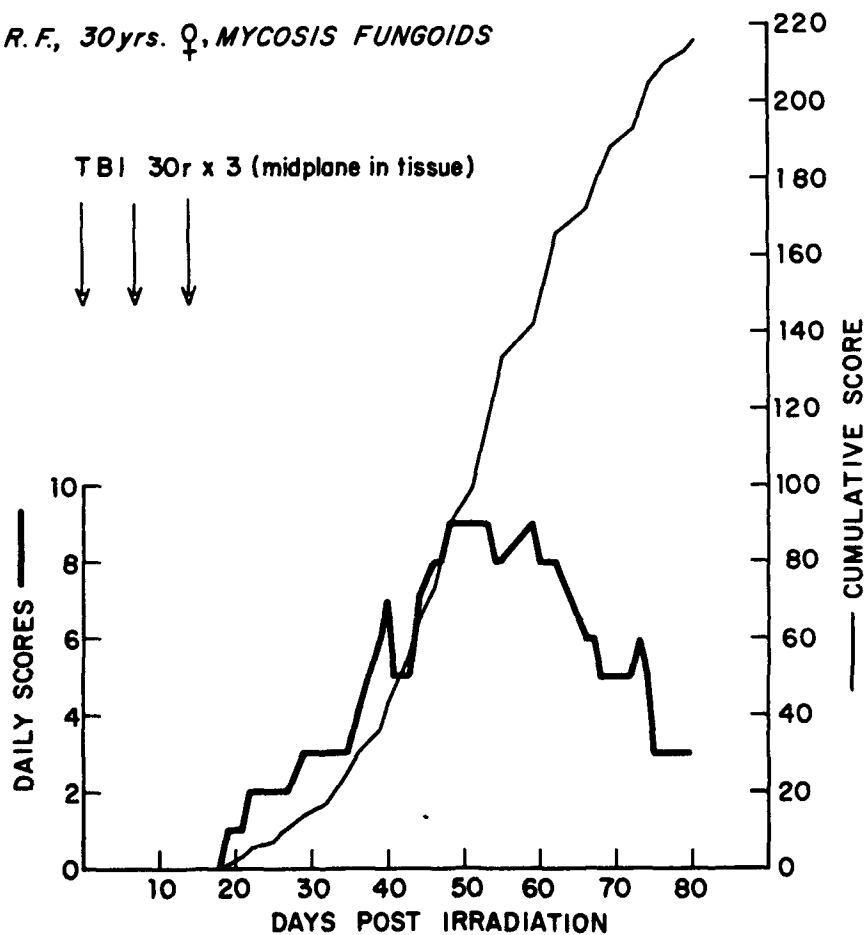
R.F., 30yrs. ♀, MYCOSES FUNGOIDES



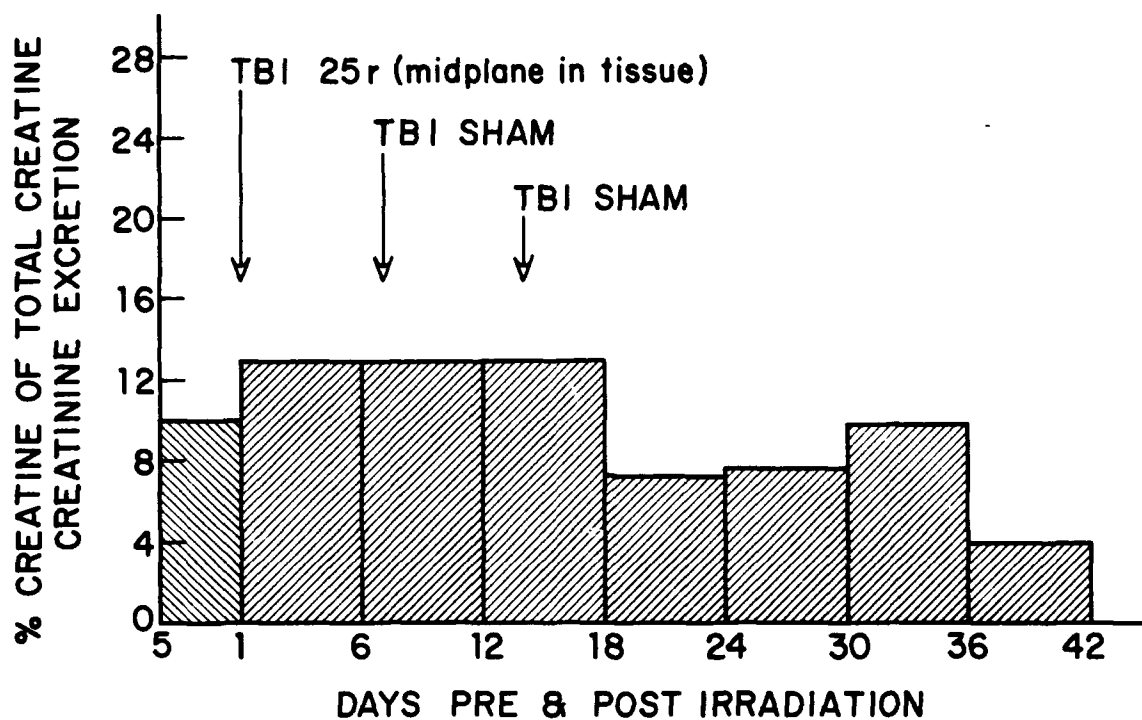
R.F., 31yrs., ♀, MYCOSIS FUNGOIDES



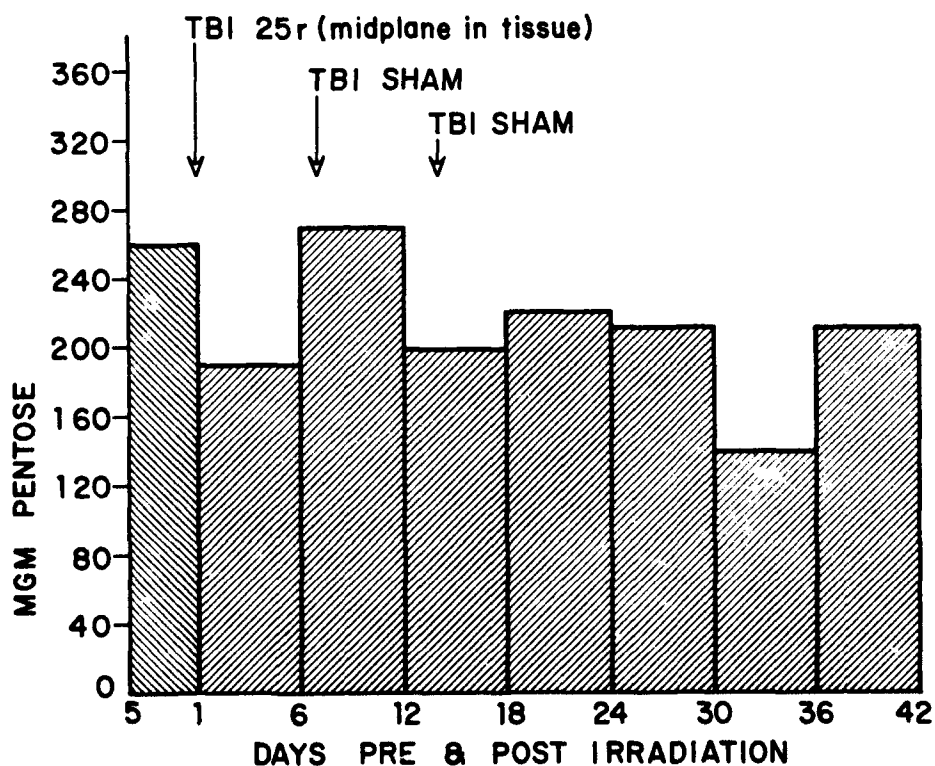
R.F., 30yrs. ♀, MYCOSIS FUNGOIDS



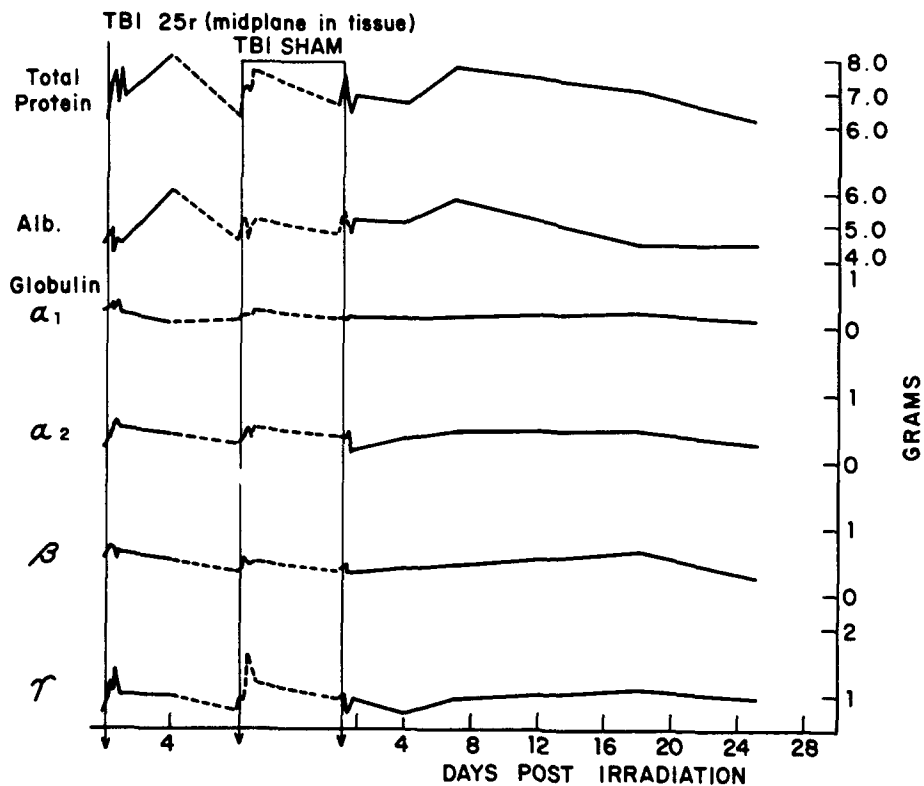
R.F., 31 yrs. ♀ MYCOSIS FUNGOIDS - PER CENT CREATINE OF TOTAL DAILY URINARY CREATINE + CREATININE



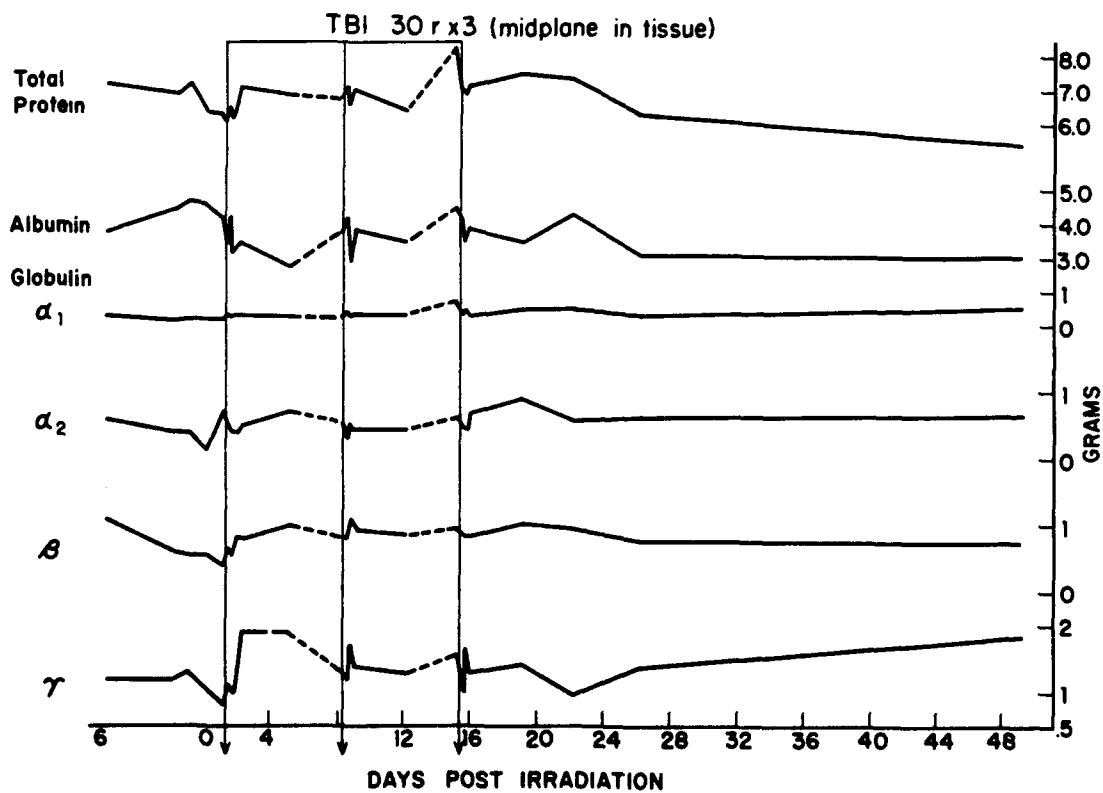
R.F., 31 yrs. ♀ MYCOSIS FUNGOIDES - AVERAGE DAILY URINARY PENTOSE EXCRETION (MGM)



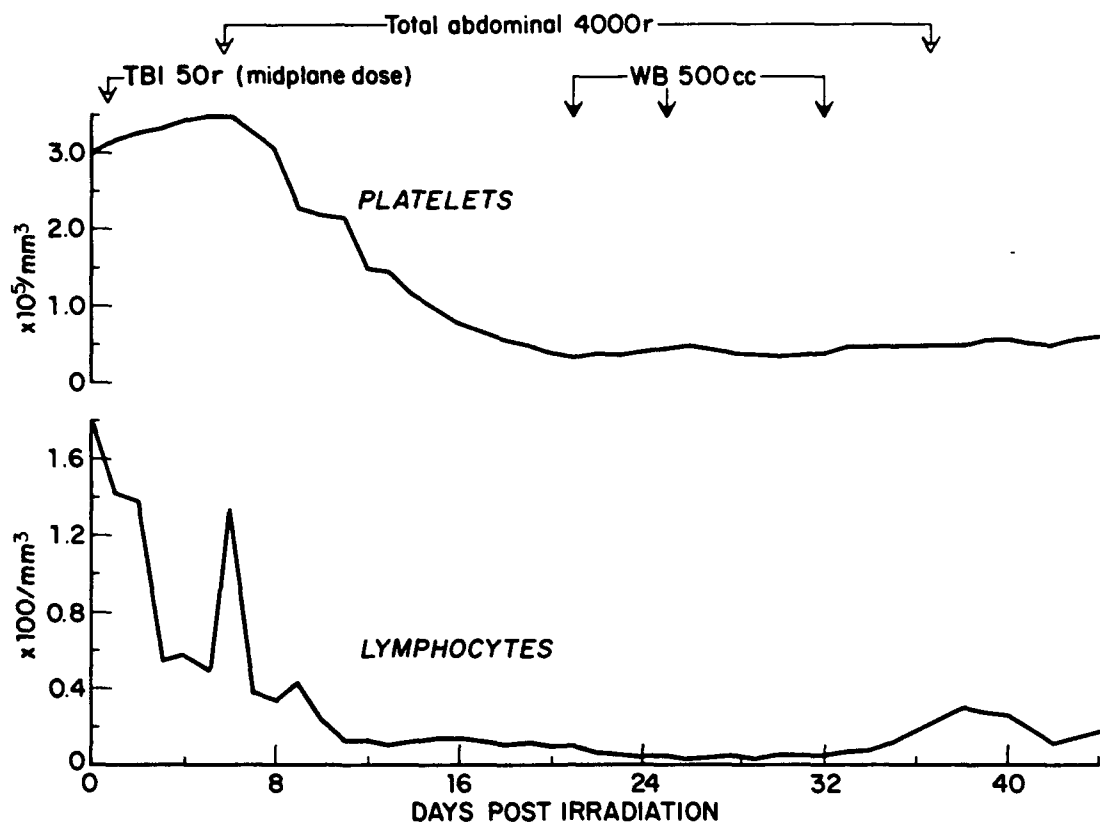
R.F., 31yrs. ♀ MYCOSIS FUNGOIDES, PLASMA PROTEIN ELECTROPHORESIS



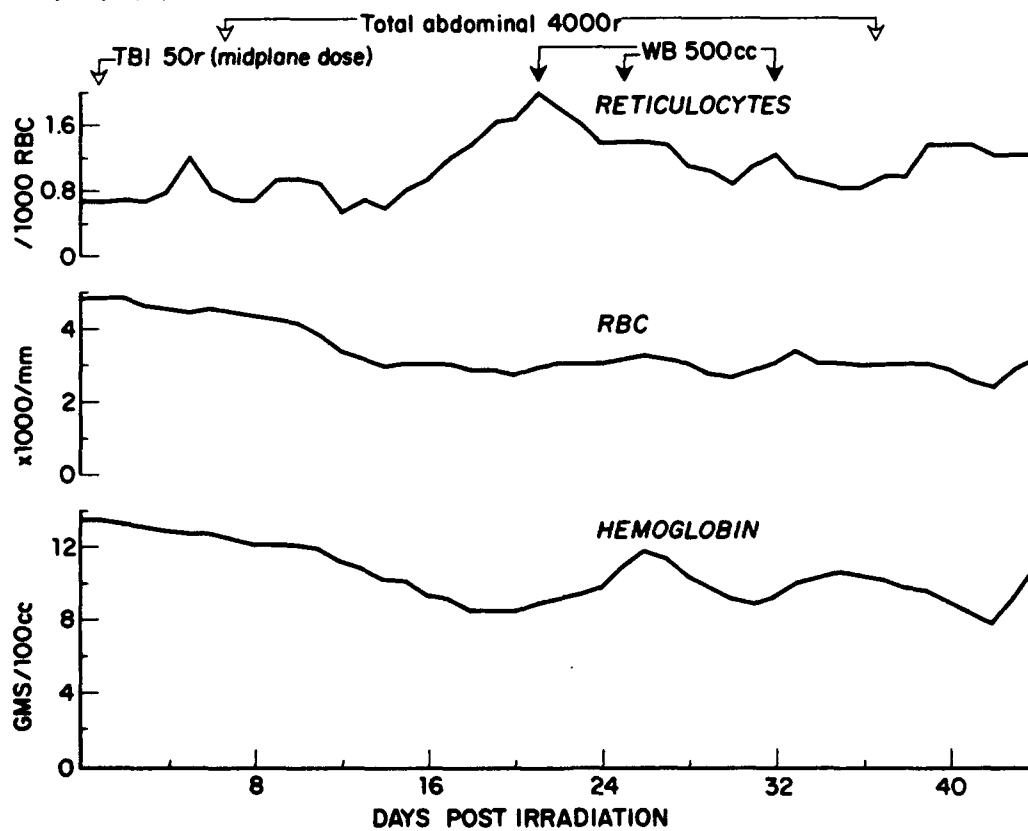
R.F., 31yrs. ♀, MYCOSES FUNGOIDES, PLASMA PROTEIN ELECTROPHORESIS



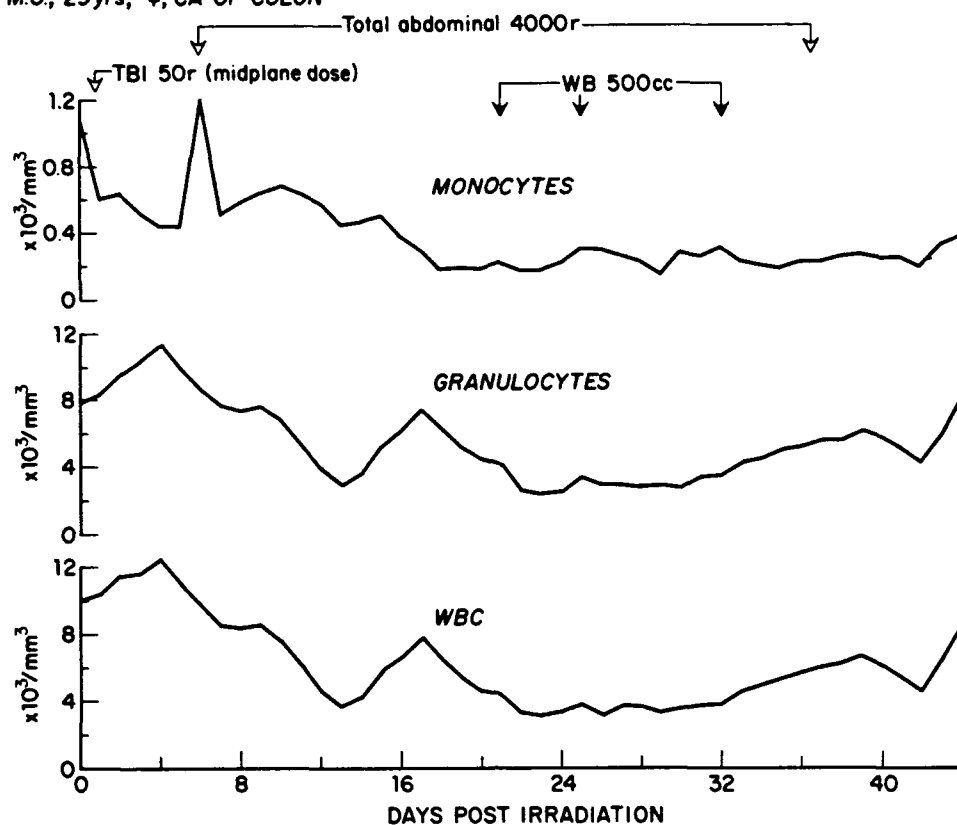
M.O., 29yrs, CA OF COLON



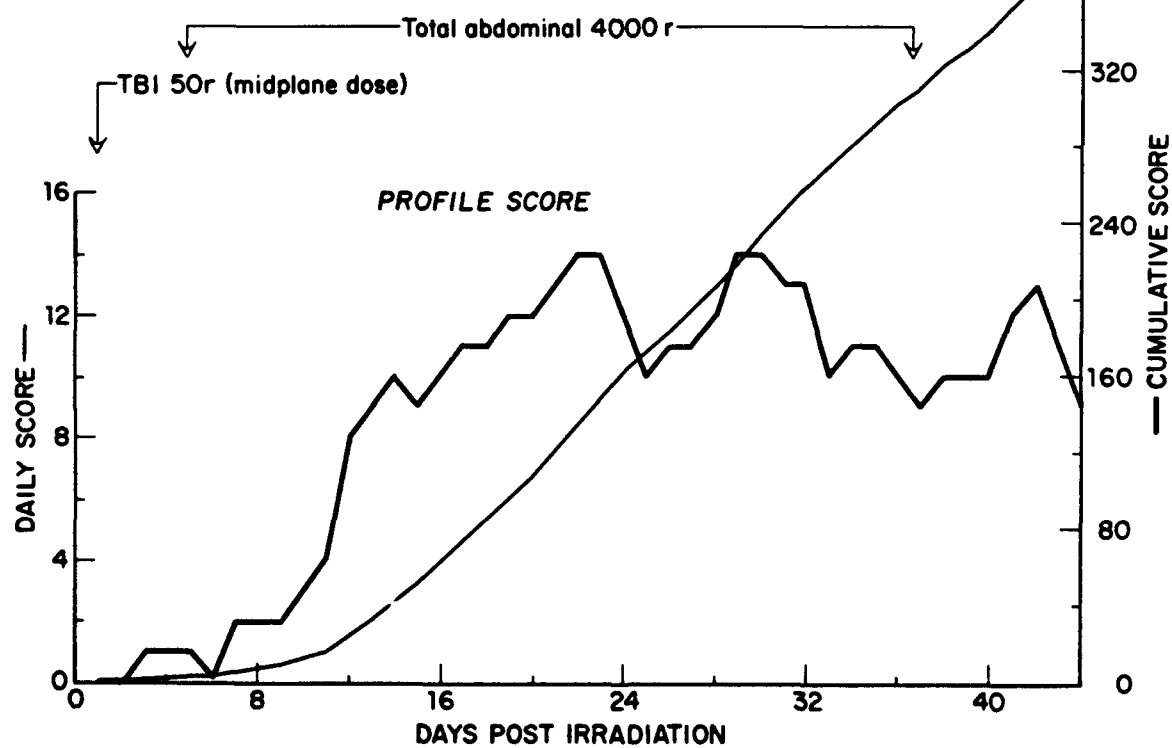
M.O., 29yrs, ♀, CA OF COLON



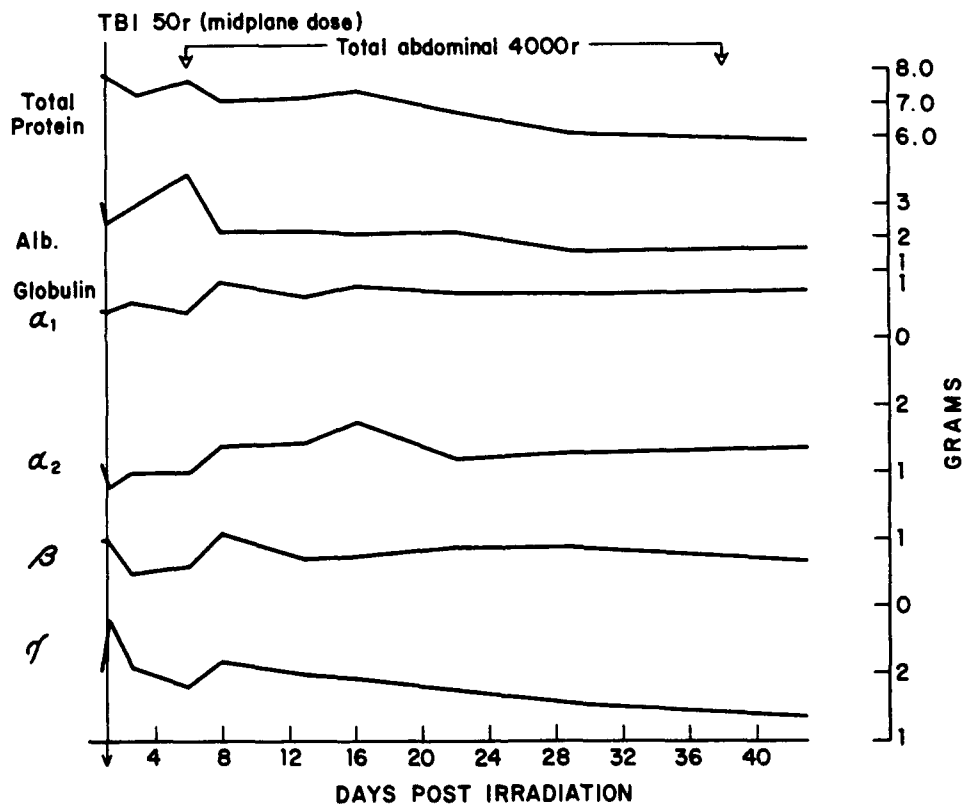
M.O., 29 yrs, ♀, CA OF COLON



M.O., 29 yrs, ♀, CA OF COLON

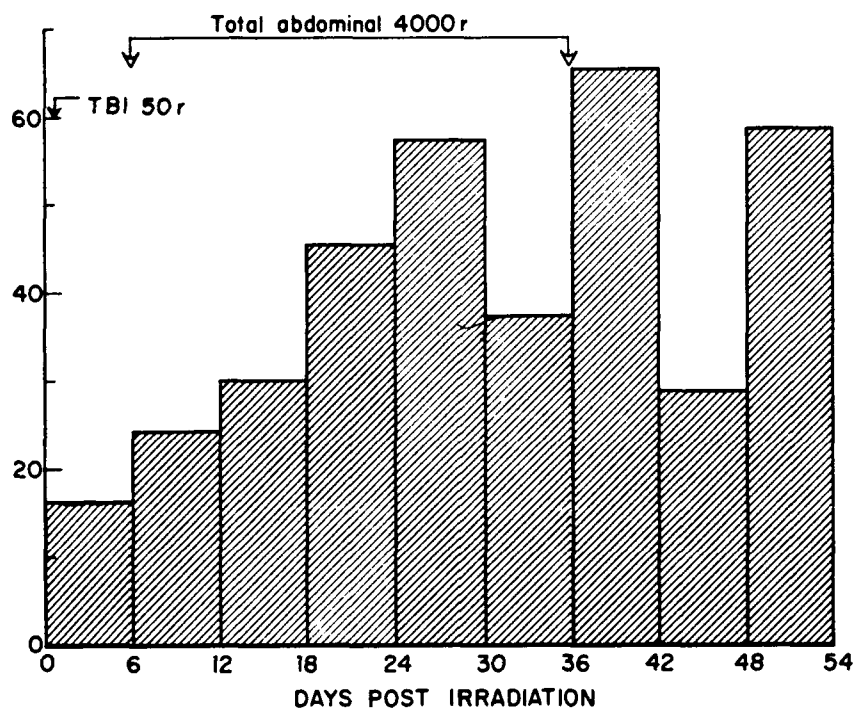


M.O., 29 yrs. ♀ CA OF COLON - PLASMA PROTEIN ELECTROPHORESIS

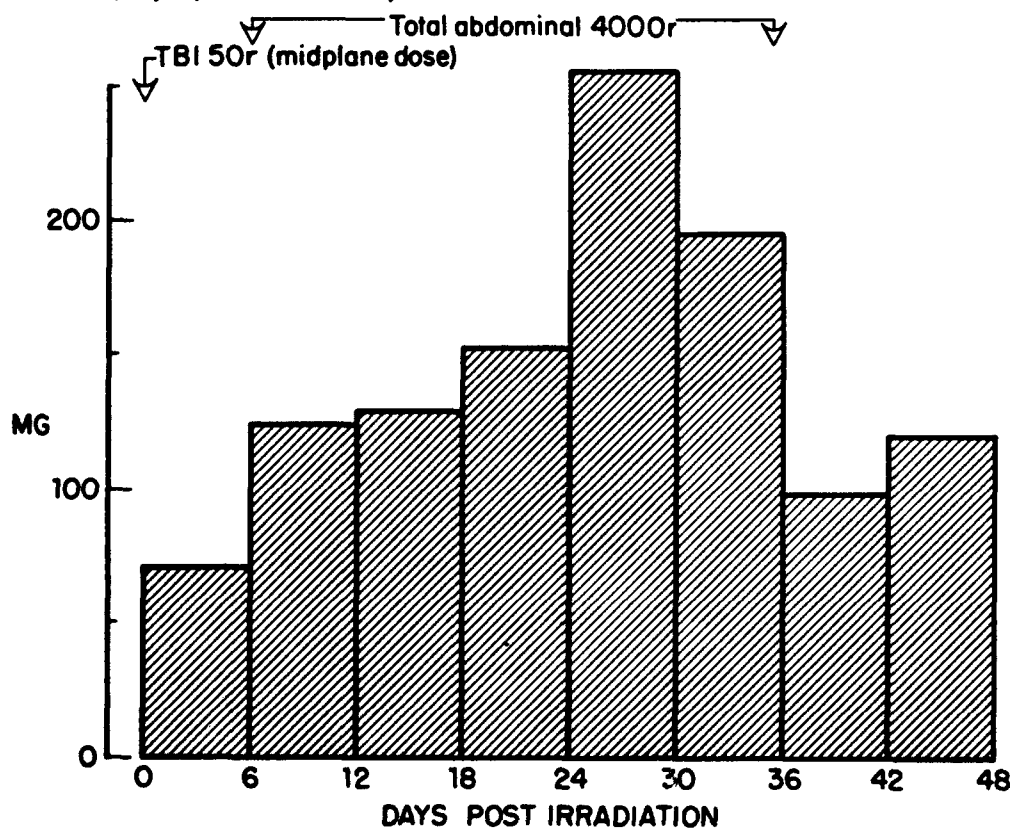


M.O., 29 yrs., ♀, CA OF COLON

PERCENT CREATINE TOTAL
DAILY URINARY CREATINE PLUS CREATININE

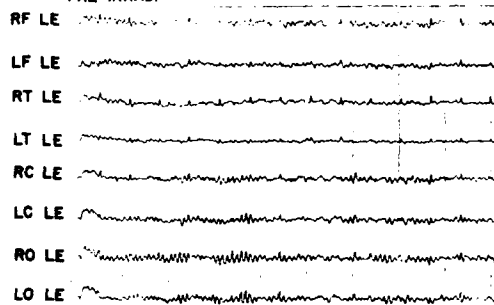


M.O. 29yrs, ♀, CA OF COLON, URINARY PENTOSE EXCRETION

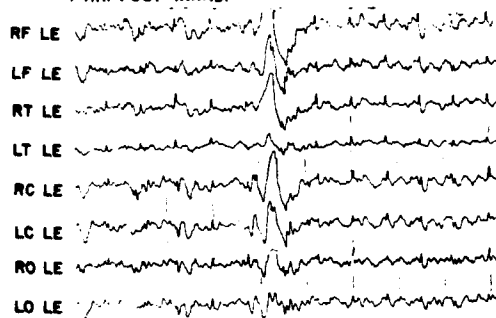


L.R. ♂ 47 YRS. 887 TOTAL BODY IRRADIATION

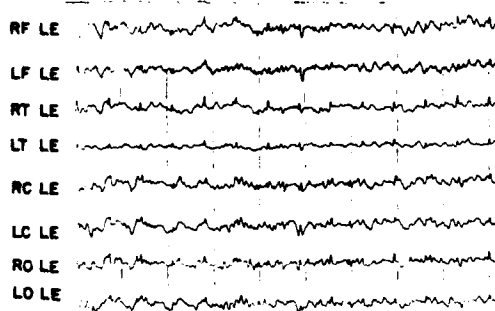
PRE IRRAD.



4 HR. POST IRRAD.

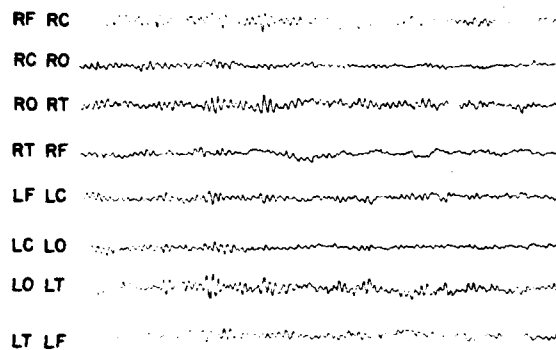


12 HR. POST IRRAD.

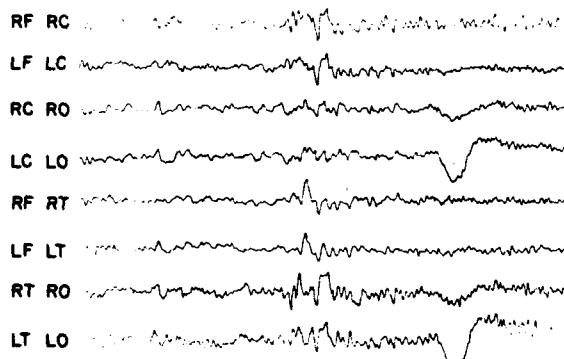


W.D. ♂ 62 YRS. 100r HEAD ONLY

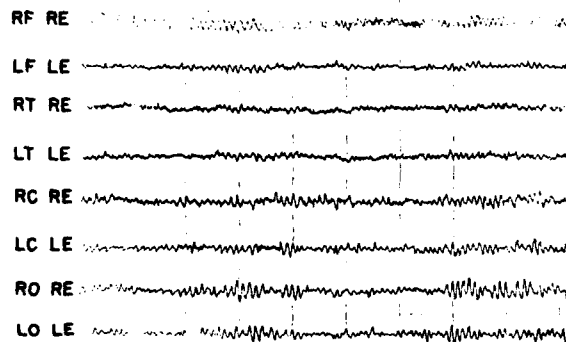
PRE IRRAD.



4 HR. POST IRRAD.



12 HR. POST IRRAD.



A.B. ♀ 44 YRS. 100 r HEAD ONLY
PRE IRRAD.

RF RE
LF LE
RT RE
LT LE
RC RE
LC LE
RO RE
LO LE

4 HR. POST IRRAD.

RF LF
RT LT
RC LC
RO LO
RE LE
LE RE
RO RF
LO LF

6 HR. POST IRRAD.

RF RE
LF LE
RT RE
LT LE
RC RE
LC LE
RO RE
LO LE