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

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Investigator: Vincent P. Collins, M. D.
Professor of Radiology
Chairman of Department of Radiology

Baylor University College of Medicine, Texas Medical Center
Houston, Texas

Jefferson Davis Hospital, 1801 Buffalo Drive
Houston, Texas

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Vincent P. Collins, M. D.

ABSTRACT

This report is made up of further observations on patients who have received total body radiation in the course of treatment for cancer of a variety of sites and types. Previously, the therapeutic aspects and biologic effects of whole body irradiation in single doses of up to 200r (measured under specified conditions) have been the principal direction of the investigation. In this report the investigation has been concerned with the effects of single doses which are well within tolerance limits or repeated small doses to observe cumulative effects or altered biologic response with protraction. This study also introduces the factor of rotation of the patient during whole body irradiation to simulate the conditions under which personnel might be exposed to uniform irradiation from all aspects.

PROGRESS

The majority of patients previously studied had been treated with whole body radiation using x-rays generated at 250 Kv and having a half value layer of 1 mm. of copper. In the past nine months, whole body irradiation has been carried out using a 2 MeV Van de Graaff x-ray generator. The conditions of exposure using 2 m v radiation are:

a) When patient is stationary -
   Target skin distance - 5 meters
   Radiation measured at skin surface with backscatter
   Order of intensity - 3r / min.

b) When patient is rotating
Target-axis distance - 4 meters
Radiation measured in air at axis of rotation
Order of intensity - 5r / min.

Data are available for comparison with other methods of description of radiation exposure.

A total of 26 patients received total body radiation and 23 of these were treated with the 2 MeV Van de Graaff unit. Of these 23 patients, only two (Ray & Koeppen) received whole body radiation as the sole method of treat ment; the remaining 21 received partial body radiation with the beam directed to the local lesion. The hematologic response of the 23 patients is shown in graphs (figures 1 - 23).

This material of itself does not introduce any new consideration in the response to total body radiation. It has been studied, however, from a number of aspects, seeking clues that would give direction to further studies.

Factors which may influence response to radiation are:

a) Age of patient

b) Concomitant disease

c) General condition of the patient

d) Blood picture before treatment

e) Partial body radiation given before, after, or at the same time as total body radiation

f) Previous treatment by chemotherapy

g) Dose and factors of total body radiation and partial body radiation

h) Anatomic site treated by partial body radiation

The importance of these factors has been considered under the following headings.

1. Effect of age on depression of white blood count in 13 patients receiving 50r total body radiation in addition to partial body radiation (see figure 24).

It is likely that age of patient does influence the recovery of leucocyte count following radiation. Observations on future patients should be planned to reveal this factor more accurately by longer follow-ups if possible.

2. A group of patients under 50 and a group of patients over 50 years of age who received whole body radiation (see figure 25).

The impression gained is in accord with the clinical observation that younger patients almost constantly show prompt recovery of leucocyte count.

3. Five patients in good general condition without generalized disease compared with six patients in poor general condition with evidence of generalized disease (see figure 26).

Although radiation exposure in this small group of patients varied, recovery of leucocyte count appears to be fairly uniform in those patients in good general condition with localized disease. It may be less certain in debilitated patients but this small number of patients does not demonstrate an impressive difference. Observations will be extended to a larger group of patients.

4. Comparison of total white blood count and lymphocyte count in patients receiving only 25r total body radiation (see figure 27).

The response at this level of dose might be expected to be inconstant and to be influenced strongly by the type of disease. This group should be extended and more thoroughly documented.

5. Comparison of white blood count response in patients receiving total body radiation plus partial body radiation to abdominal region with patients receiving only partial body radiation to abdominal region (see figure 28).

In two groups of five patients each, it is not evident that 50r total body radiation has increased depression of white blood count or delayed recovery.

6. Comparison of white blood count response in patients receiving total body radiation plus partial body radiation to thorax with patients receiving only partial body radiation to thorax (see figure 29).

In two groups of six patients each, there is no evidence that 50r total body radiation increased depression of white blood count or delayed recovery.

A comparison of figures 28 and 29 does not indicate a difference between patients receiving radiation to thorax and those receiving radiation to the abdomen; 50r whole body radiation is not shown to increase depression of white cell count or delay recovery in either group.

Although no immediate effect has been found that can be ascribed to 50r whole body radiation, the number of patients so treated should be increased and duration of observation of blood response prolonged. If these initial impressions are confirmed, the dose of whole body radiation can be increased.

7. Comparison of patients receiving total body radiation by rotation and by stationary fields (see figures 30 A. and 30 B).

For the levels of radiation exposure indicated on the graphs, the impression gained is that rotation does not appreciably alter the hematologic response.

TABLE I

RADIATION REACTION FOLLOWING TOTAL BODY RADIATION AND PARTIAL BODY RADIATION

Dose	No Nausea & Vomiting	Nausea Only	Nausea & Vomiting
25r	3	0	0
50r	12	1	3
75r	3	0	0
100r	1	0	0
Total	19	1	3

It is our impression that for levels of total body radiation below 100r, symptoms which might be ascribed to radiation sickness are so mild as to be clinically unimportant. When symptoms are mild, the relation to radiation is never certain because manifestations lie within the range of individual patient response to deliberate or involuntary suggestion.

Twenty-five patients treated by total body radiation received tetanus toxoid. Three of these were treated by conventional (250 Kv) unit, while 22 were treated by the 2 MeV Van de Graaff unit. This aspect was carried out in collaboration with the Division of Physiology and Pharmacology at Walter Reed Army Institute of Research. The patients selected for this study were those having a history of previous tetanus immunization. Tetanus toxoid (0.5 cc) as a booster was given intramuscularly following total body radiation. Blood specimens (5 cc) were drawn just prior to the booster dose and on the 6th and 14th day after immunization. The purpose of this study was to determine whether total body radiation in doses of less than 100r influence immunologic

response. The sera collected were sent to Walter Reed Army Institute of Research.

FUTURE

Investigations will be continued along the following lines.

1. Effect of total body radiation in doses of 50r. A dose of 50r is a likely arbitrary maximum figure to be placed upon deliberate or voluntary exposure under emergency circumstances. Initial impressions indicate that this will produce no clearly recognizable clinical or laboratory effect of an immediate type. The number of observations bearing on this view should be increased to justify a firm conclusion. At the same time, doses of total body radiation of this magnitude will be combined with a therapeutic course of partial body radiation to establish whether there is a masked or latent effect that might be revealed by a therapeutic course of partial body radiation.

2. Effect of whole body radiation delivered by stationary fields compared with radiation delivered during rotation. Comparison at this time indicates no recognizable difference in the hematologic response for doses of total body radiation in the range of dose investigated.

The number of patients available for comparison will be increased and as the lack of augmenting effect is confirmed, the dose will be increased.

3. Protracted weekly exposures in doses of the order of 10 to 25r are planned for patients who might benefit by long continued radiation.

4. The physical set up for extra-corporeal radiation of circulating blood in dogs has been completed. The conditions of the present experiment are intended to simulate protection of the whole body except for one tissue (Circulating blood) and would be the reciprocal of whole body radiation with

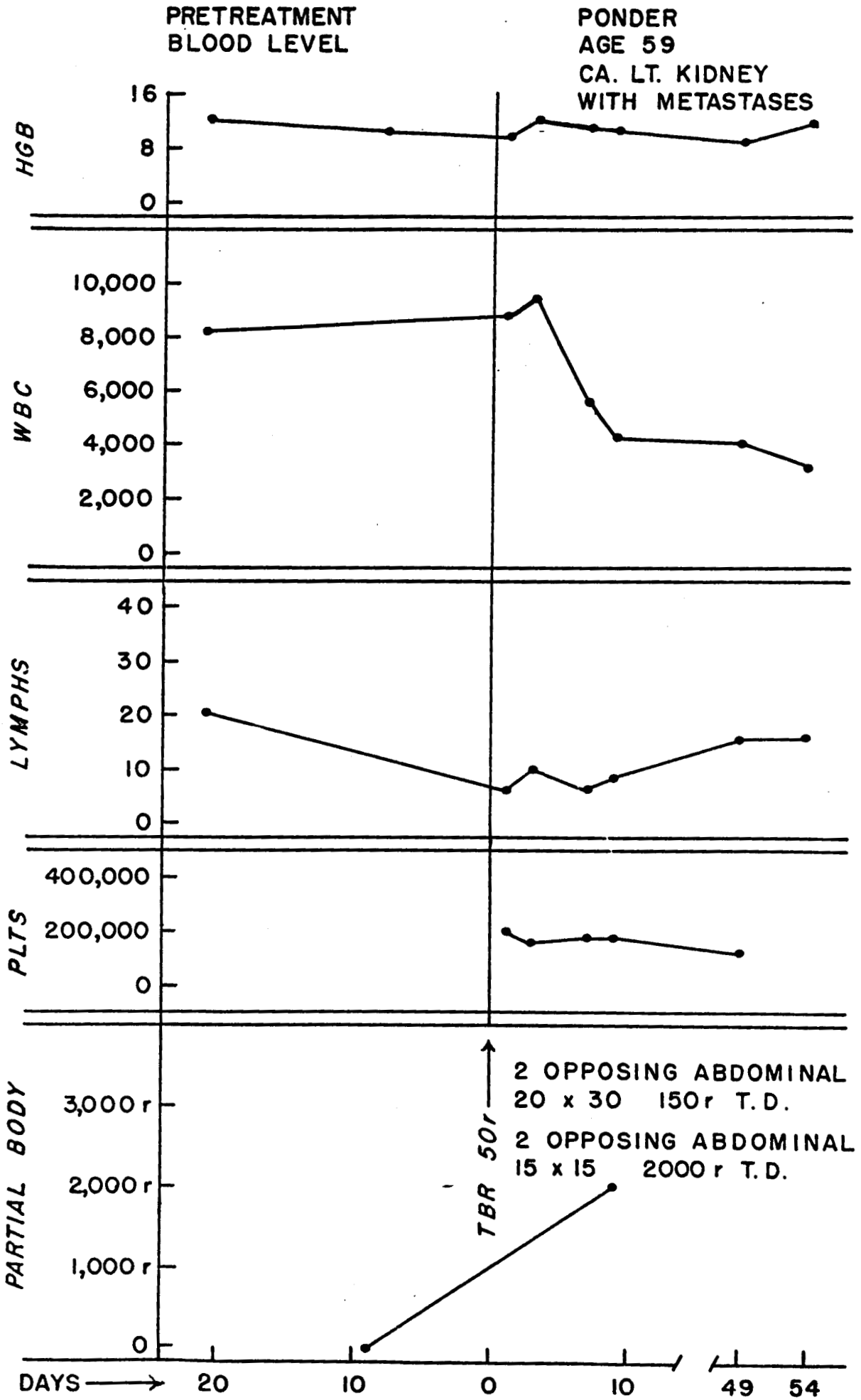
one tissue (spleen) protected. Measurements indicate that it is possible to give circulating blood an exposure of up to 10,000r in a period of 30 minutes.

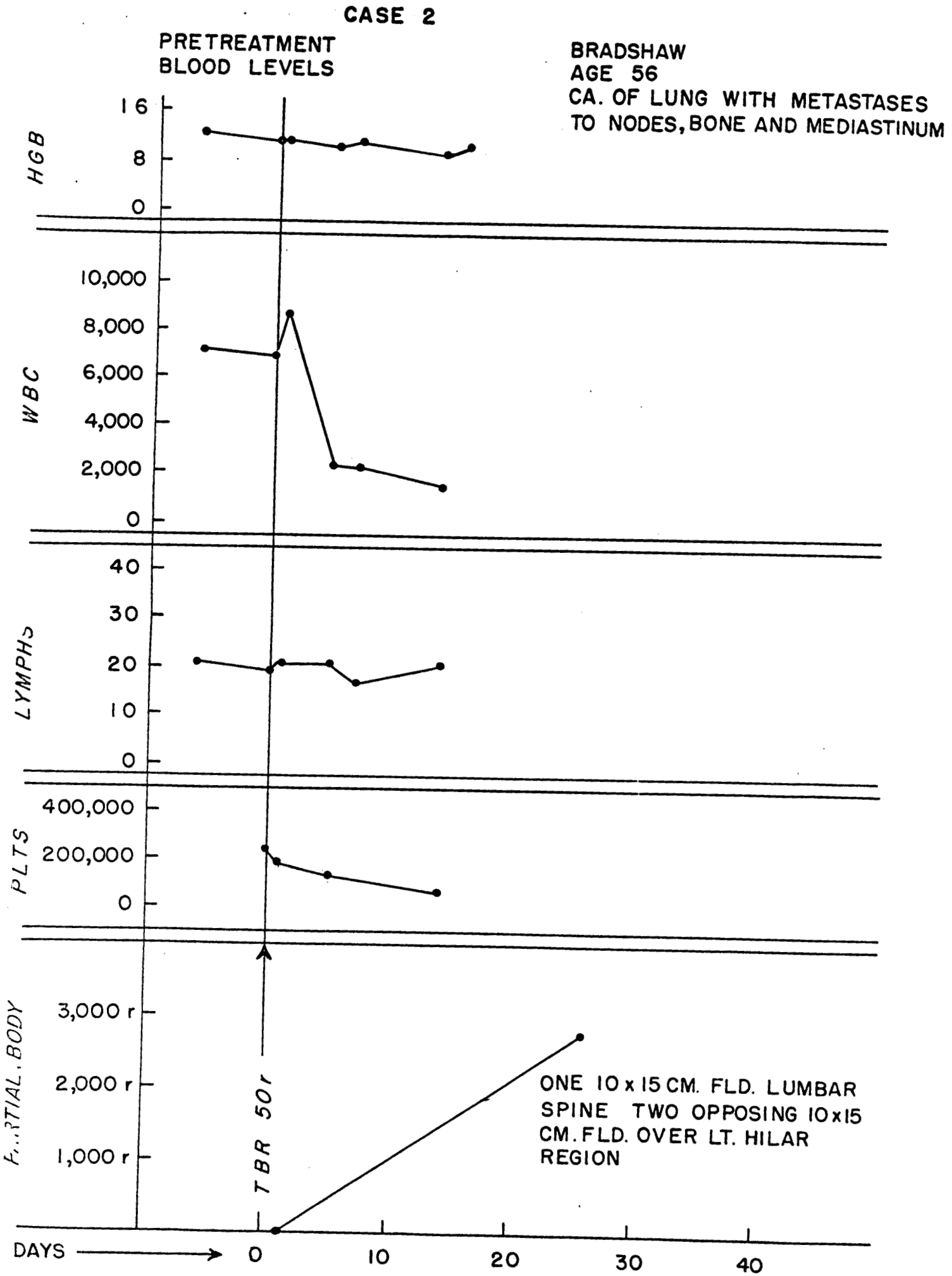
5. Material will be obtained to extend the observations on influence of total body radiation on the immunologic response to tetanus toxoid.

REFERENCE

V. P. Collins and R. K. Loeffler. The Therapeutic Use of Single Doses of Total Body Radiation. Am. J. Roentgenol. 75:542-547, 1956.

CASE I

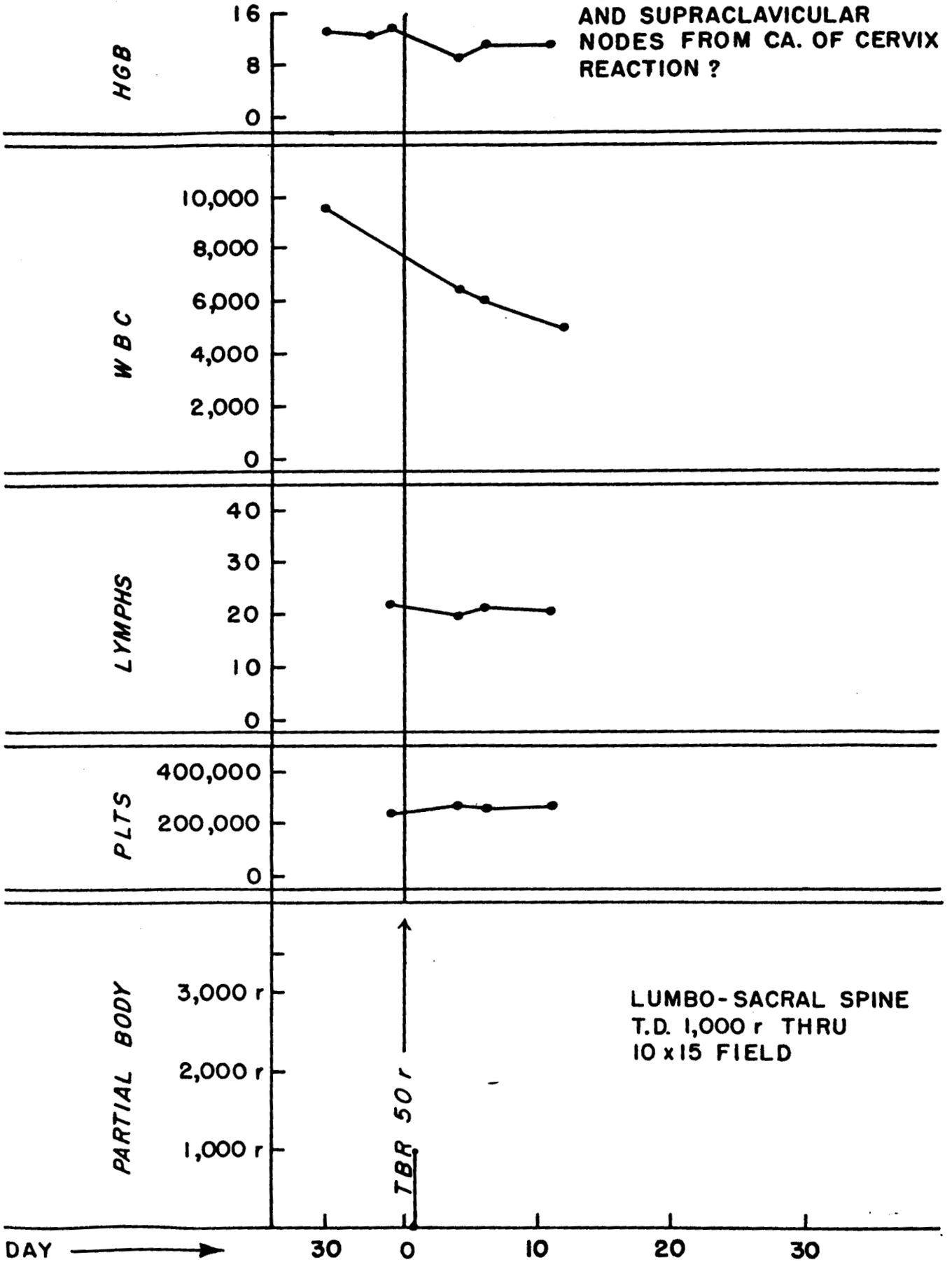

PRETREATMENT
BLOOD LEVEL
PONDER
AGE 59
CA. LT. KIDNEY
WITH METASTASES
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
3,000 r
2,000 r
1,000 r
0
TBR 50r
2 OPPOSING ABDOMINAL
20 x 30 150r T.D.
2 OPPOSING ABDOMINAL
15 x 15 2000 r T.D.
DAYS
20
10
0
10
49
54


CASE 2
PRETREATMENT
BLOOD LEVELS
BRADSHAW
AGE 56
CA. OF LUNG WITH METASTASES
TO NODES, BONE AND MEDIASTINUM
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
3,000 r
2,000 r
1,000 r
TBR 50r
ONE 10 x 15 CM. FLD. LUMBAR
SPINE TWO OPPOSING 10x15
CM. FLD. OVER LT. HILAR
REGION
DAYS
0
10
20
30
40

CASE 3

PRETREATMENT BLOOD LEVELS

McCOMMAS #157
AGE 47
METASTASES TO SPINE AND SUPRACLAVICULAR NODES FROM CA. OF CERVIX
REACTION ?



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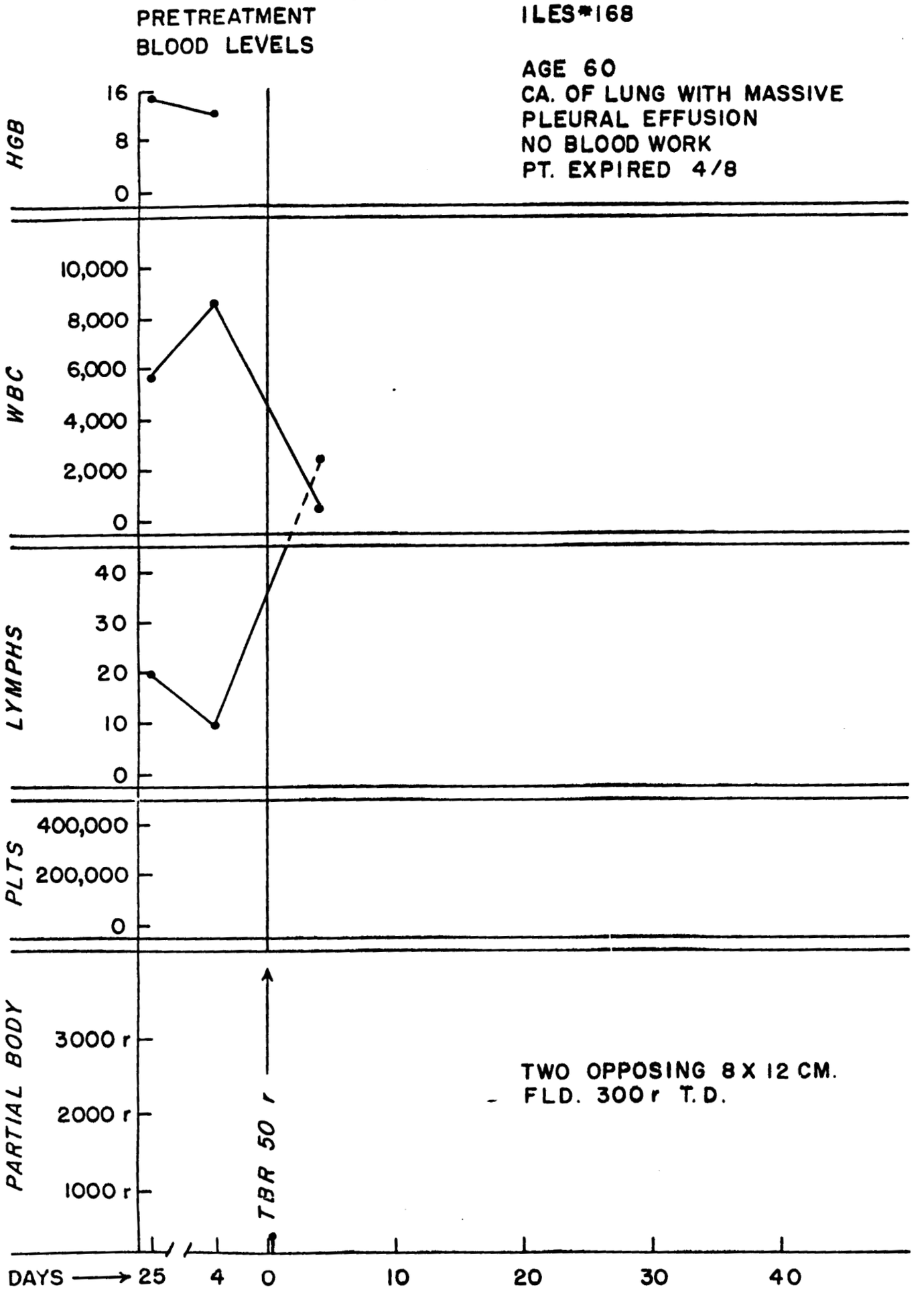
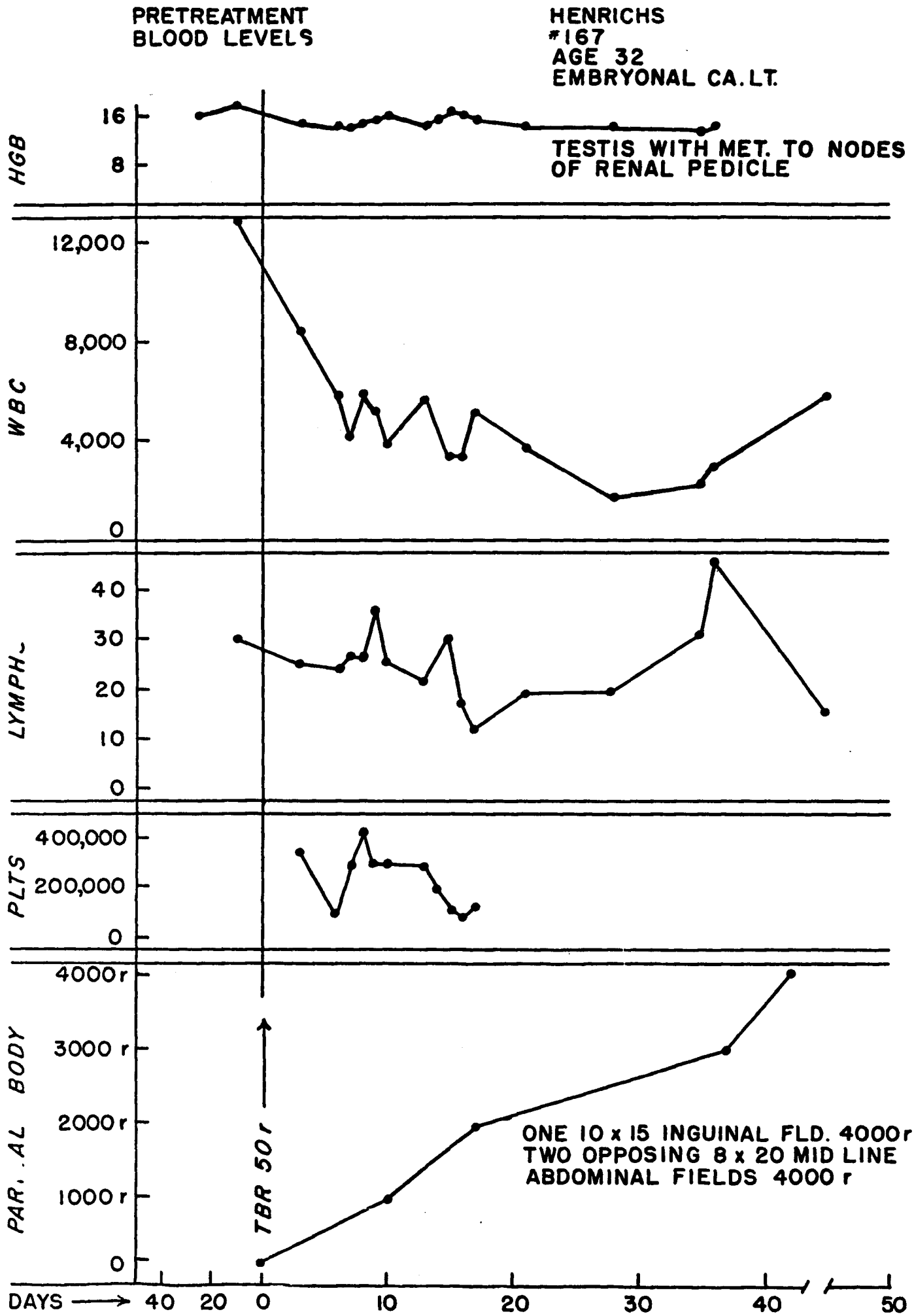
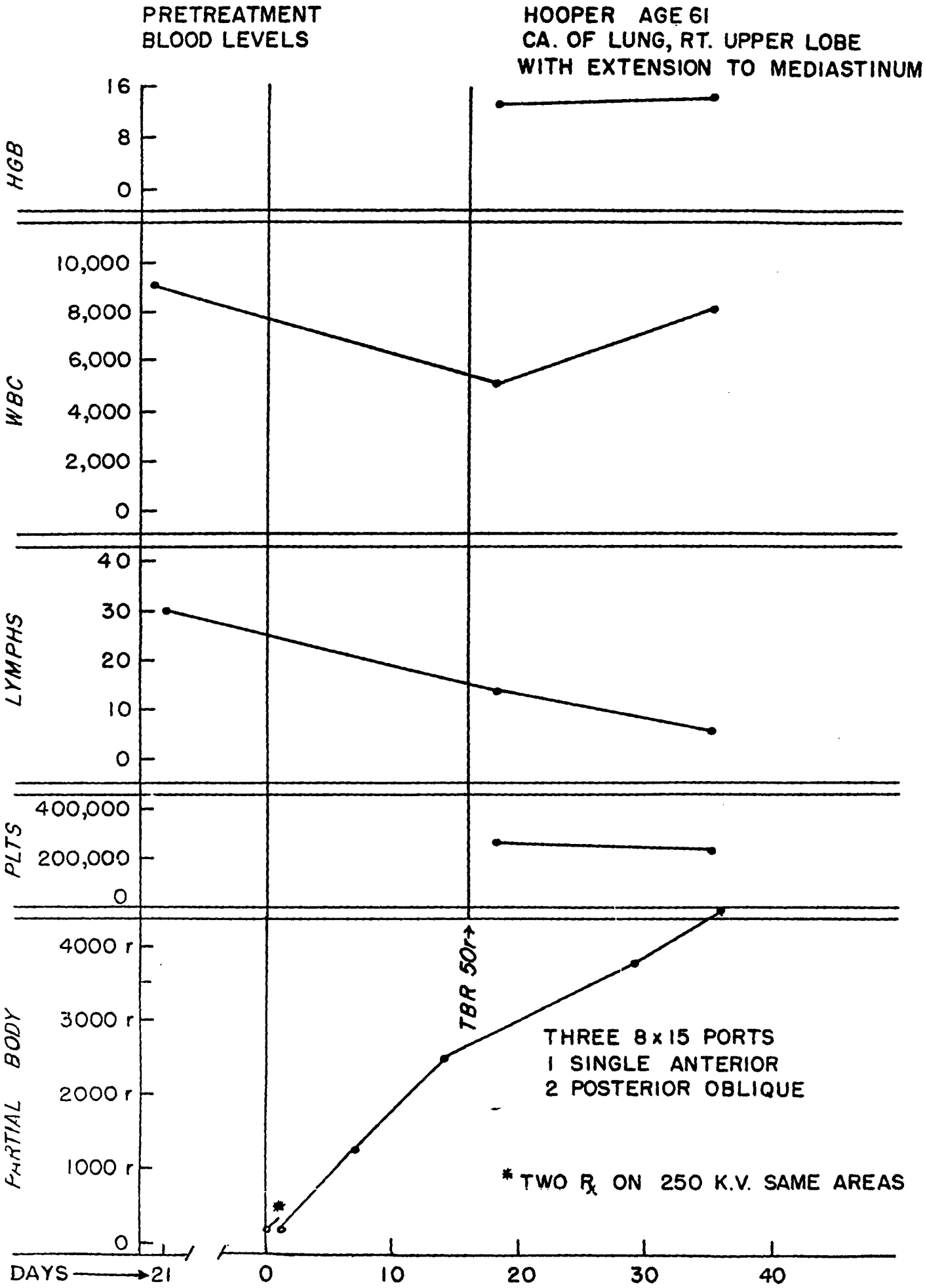
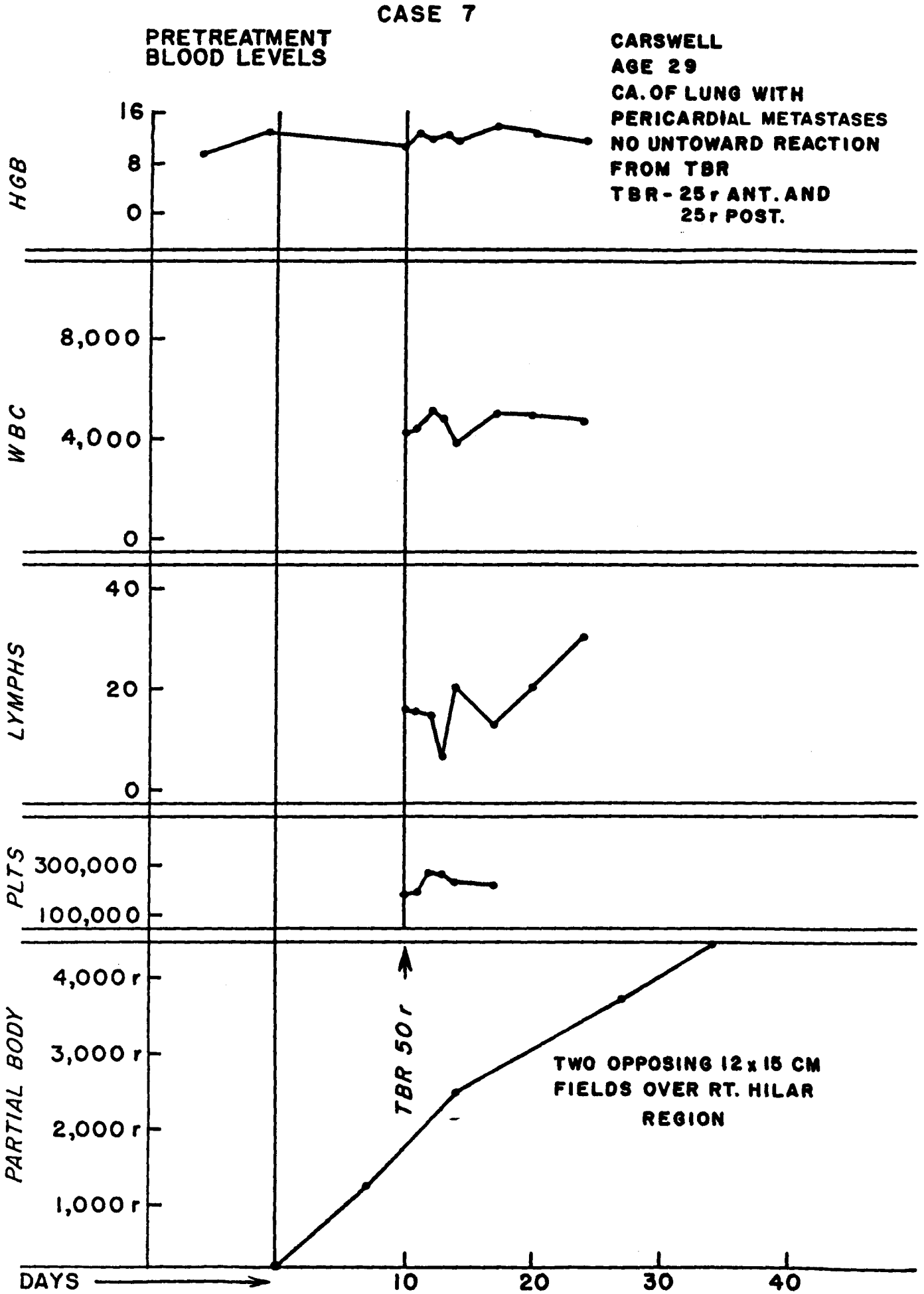

PRETREATMENT
BLOOD LEVELS
ILES#168
AGE 60
CA. OF LUNG WITH MASSIVE
PLEURAL EFFUSION
NO BLOOD WORK
PT. EXPIRED 4/8
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
3000 r
2000 r
1000 r
TBR 50 r
TWO OPPOSING 8 X 12 CM.
FLD. 300 r T.D.
DAYS
25
4
0
10
20
30
40

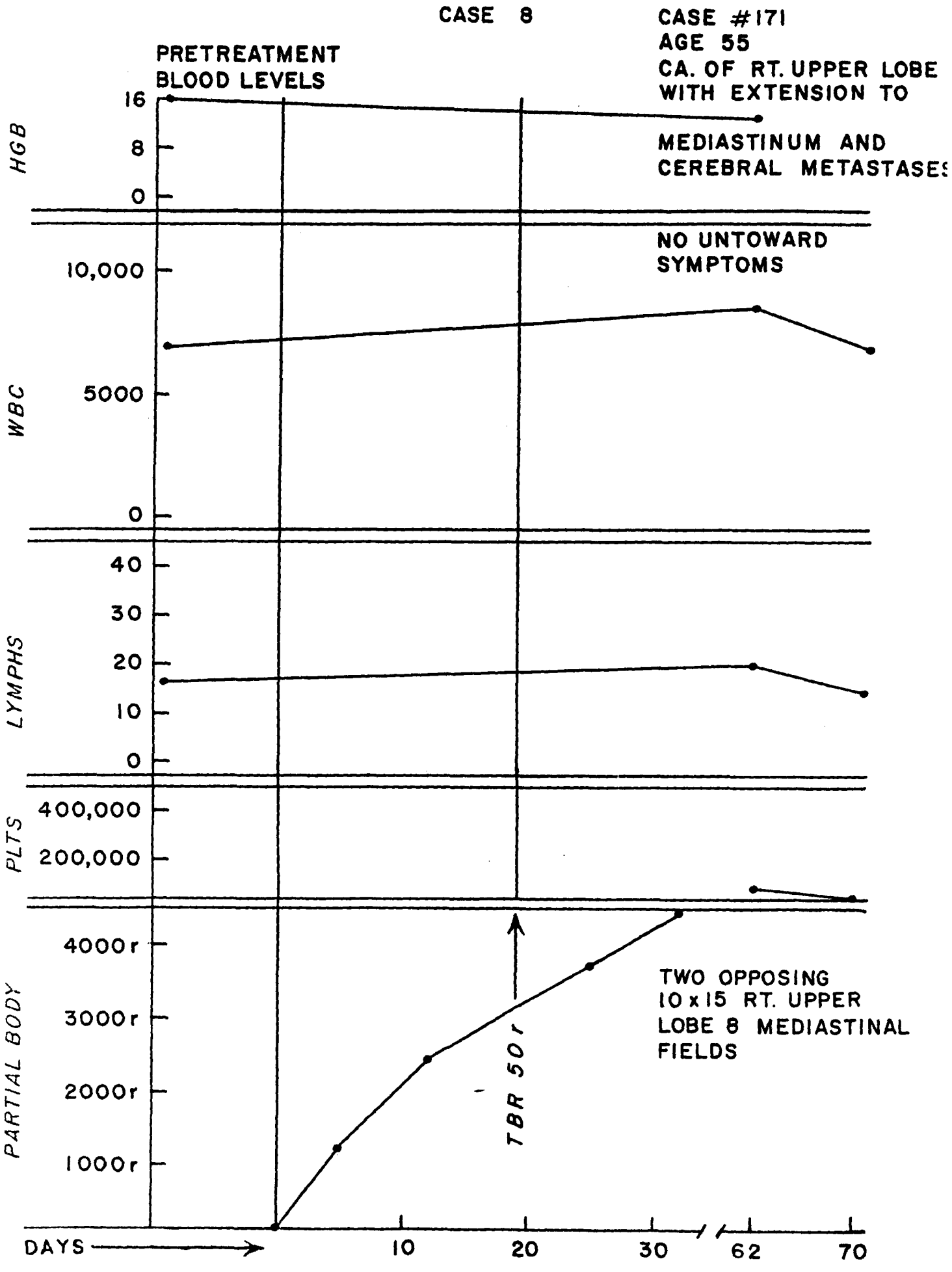
CASE 5


PRETREATMENT
BLOOD LEVELS
HENRICHS
#167
AGE 32
EMBRYONAL CA. LT.
TESTIS WITH MET. TO NODES
OF RENAL PEDICLE
HGB
16
8
WBC
12,000
8,000
4,000
0
LYMPH.
40
30
20
10
0
PLTS
400,000
200,000
0
PAR. AL BODY
4000 r
3000 r
2000 r
1000 r
0
TBR 50 r
ONE 10 x 15 INGUINAL FLD. 4000 r
TWO OPPOSING 8 x 20 MID LINE
ABDOMINAL FIELDS 4000 r
DAYS
40
20
0
10
20
30
40
50

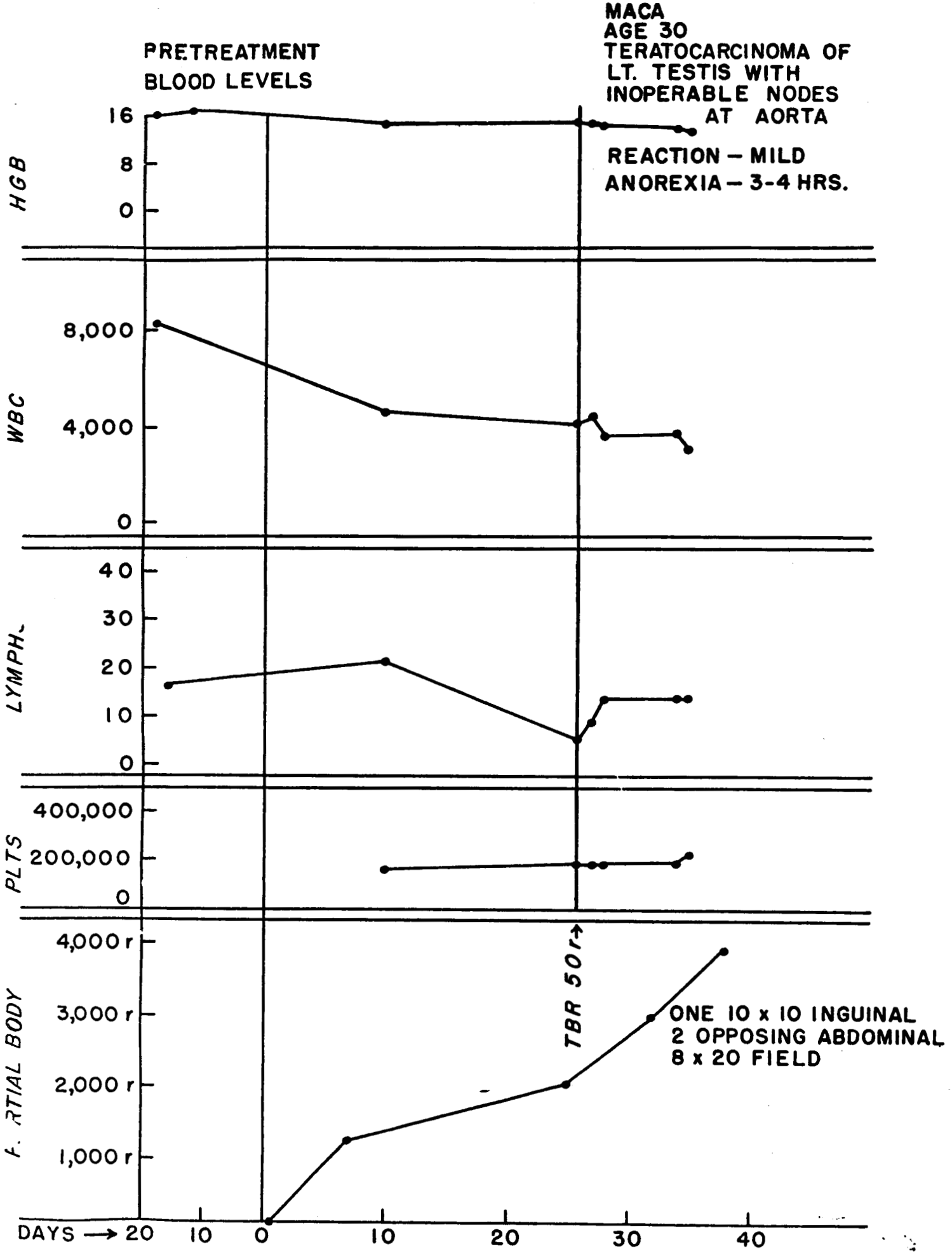
CASE 6


PRETREATMENT
BLOOD LEVELS
HOOPER AGE 61
CA. OF LUNG, RT. UPPER LOBE
WITH EXTENSION TO MEDIASTINUM
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
4000 r
3000 r
2000 r
1000 r
0
TBR 50r→
THREE 8 x 15 PORTS
1 SINGLE ANTERIOR
2 POSTERIOR OBLIQUE
* TWO Rx ON 250 K.V. SAME AREAS
DAYS →
21
0
10
20
30
40

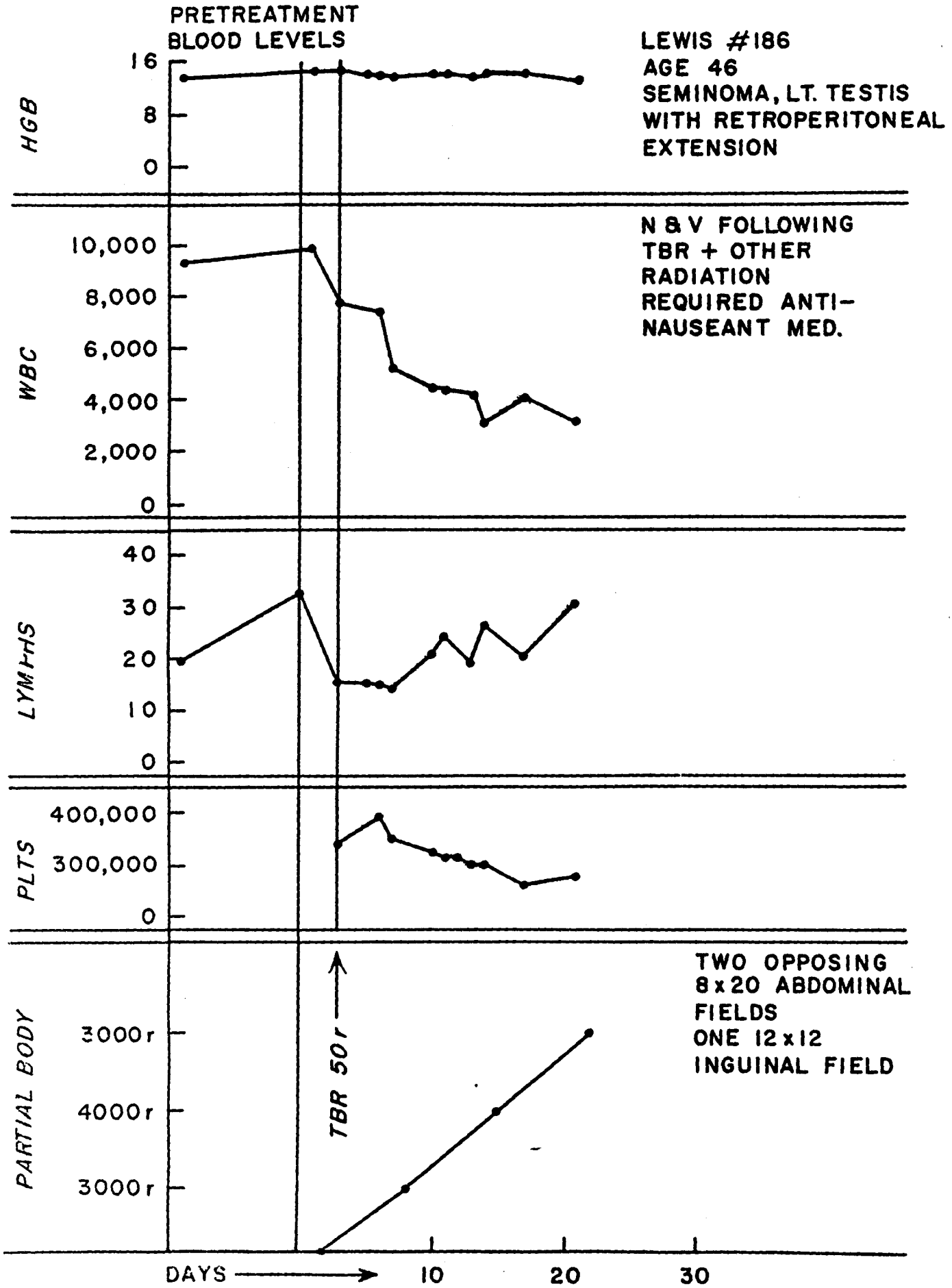

CASE 7
PRETREATMENT BLOOD LEVELS
CARSWELL
AGE 29
CA. OF LUNG WITH PERICARDIAL METASTASES
NO UNTOWARD REACTION FROM TBR
TBR - 25 r ANT. AND 25 r POST.
HGB
16
8
0
WBC
8,000
4,000
0
LYMPHS
40
20
0
PLTS
300,000
100,000
PARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
TBR 50 r
TWO OPPOSING 12 x 15 CM FIELDS OVER RT. HILAR REGION
DAYS
10
20
30
40


CASE 8
CASE #171
AGE 55
CA. OF RT. UPPER LOBE
WITH EXTENSION TO
MEDIASTINUM AND
CEREBRAL METASTASES
PRETREATMENT
BLOOD LEVELS
HGB
16
8
0
NO UNTOWARD
SYMPTOMS
WBC
10,000
5000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
PARTIAL BODY
4000r
3000r
2000r
1000r
TBR 50r
TWO OPPOSING
10x15 RT. UPPER
LOBE & MEDIASTINAL
FIELDS
DAYS
10
20
30
62
70

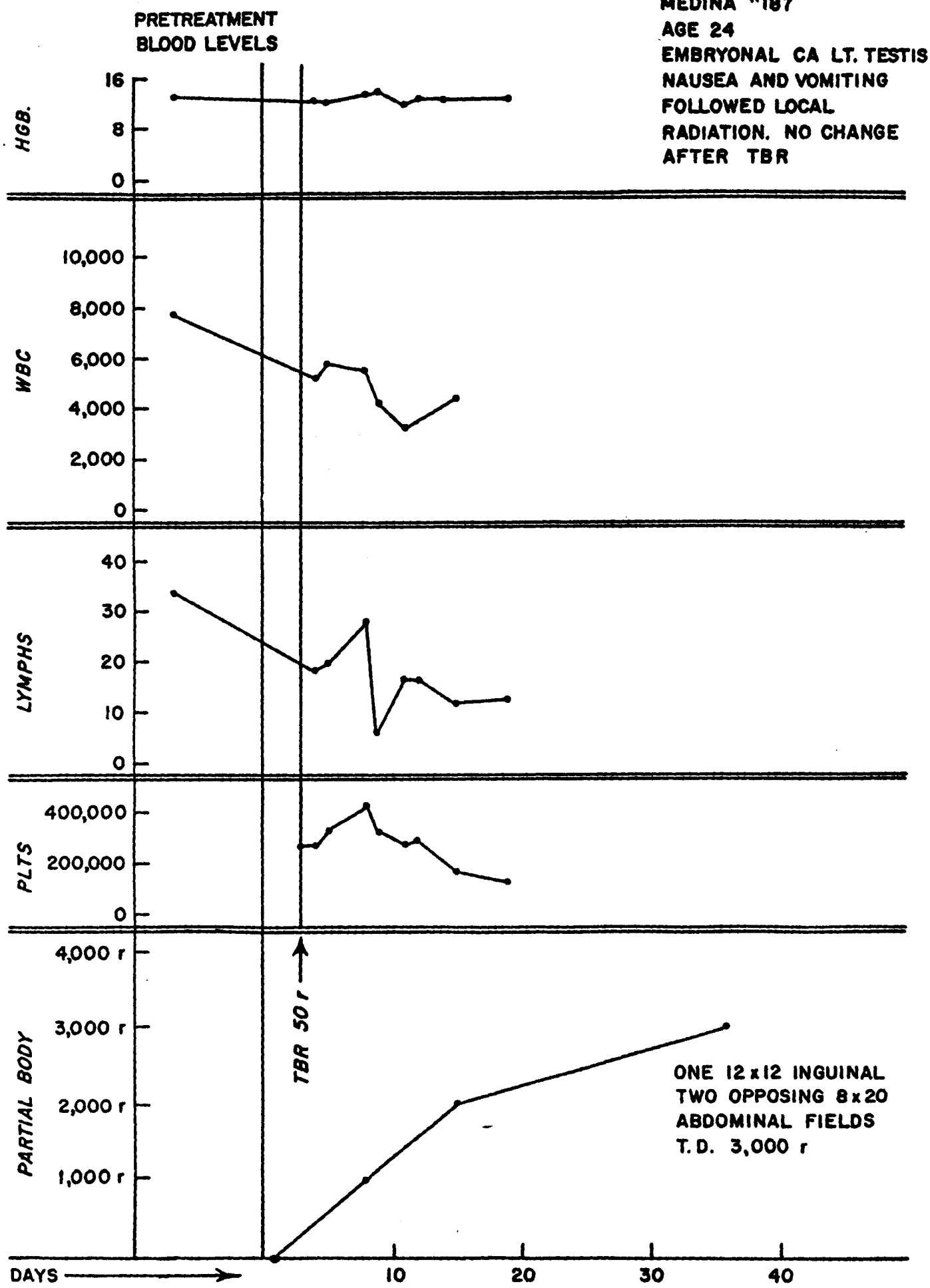
CASE 9


MACA
AGE 30
TERATOCARCINOMA OF
LT. TESTIS WITH
INOPERABLE NODES
AT AORTA
PRETREATMENT
BLOOD LEVELS
REACTION – MILD
ANOREXIA – 3-4 HRS.
HGB
16
8
0
WBC
8,000
4,000
0
LYMPH.
40
30
20
10
0
PLTS
400,000
200,000
0
F. ARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
TBR 50 r
ONE 10 x 10 INGUINAL
2 OPPOSING ABDOMINAL
8 x 20 FIELD
DAYS → 20
10
0
10
20
30
40

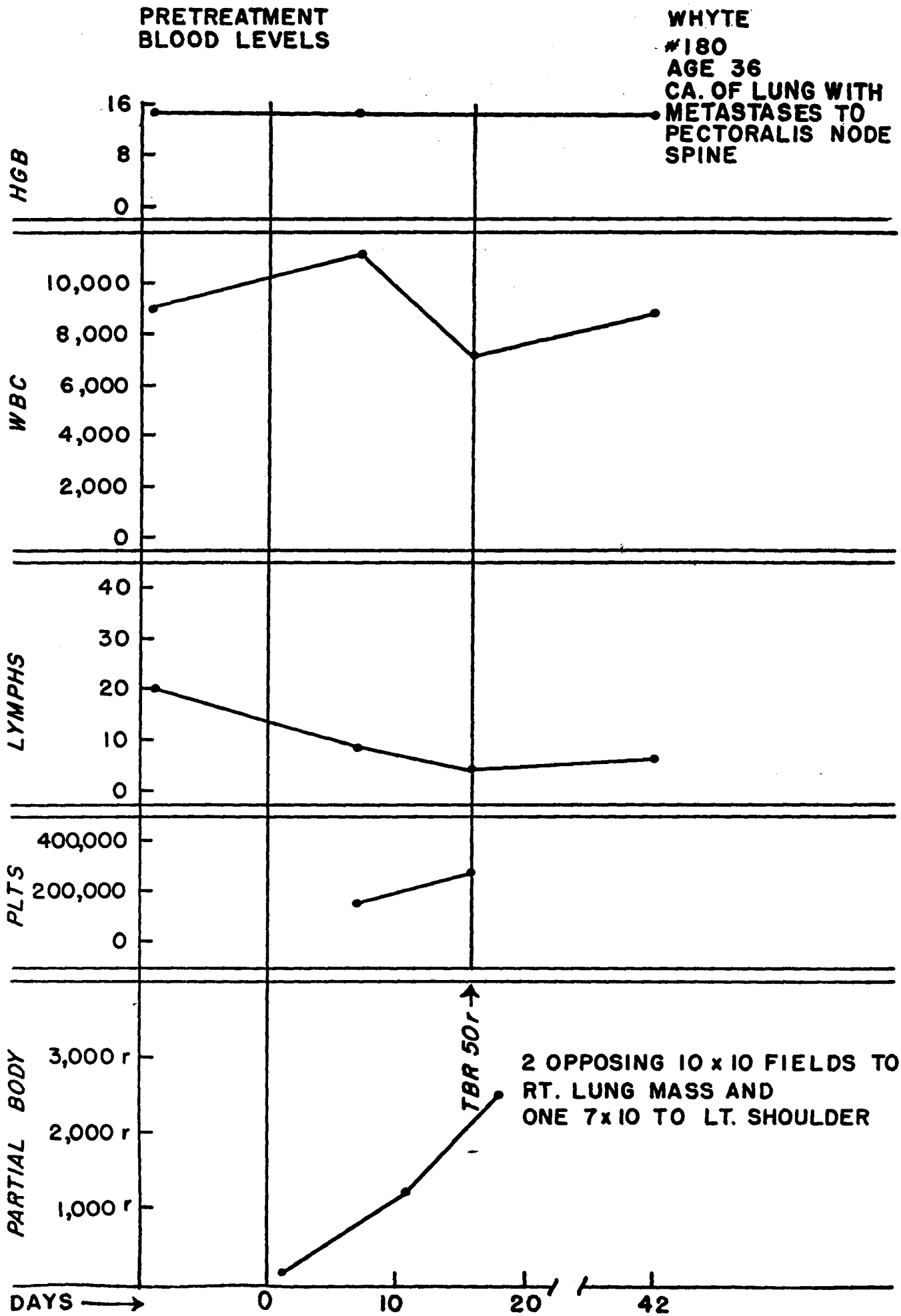
CASE 10


PRETREATMENT
BLOOD LEVELS
LEWIS #186
AGE 46
SEMINOMA, LT. TESTIS
WITH RETROPERITONEAL
EXTENSION
HGB
16
8
0
N & V FOLLOWING
TBR + OTHER
RADIATION
REQUIRED ANTI-
NAUSEANT MED.
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
300,000
0
TWO OPPOSING
8 x 20 ABDOMINAL
FIELDS
ONE 12 x 12
INGUINAL FIELD
PARTIAL BODY
3000r
4000r
3000r
TBR 50r
DAYS
10
20
30

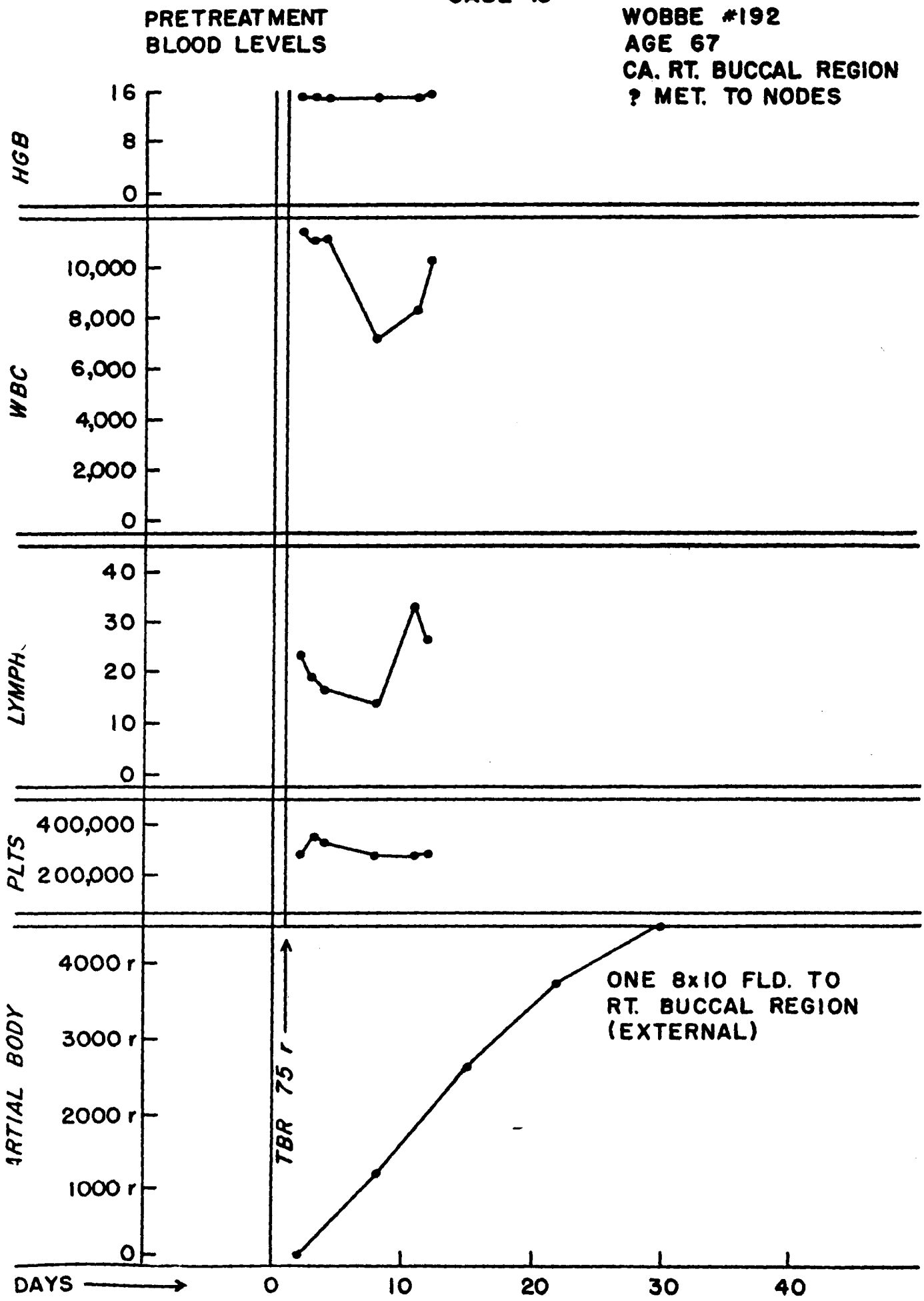
CASE II


PRETREATMENT
BLOOD LEVELS
MEDINA #187
AGE 24
EMBRYONAL CA LT. TESTIS
NAUSEA AND VOMITING
FOLLOWED LOCAL
RADIATION. NO CHANGE
AFTER TBR
HGB.
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
TBR 50 r
ONE 12 x 12 INGUINAL
TWO OPPOSING 8 x 20
ABDOMINAL FIELDS
T.D. 3,000 r
DAYS
10
20
30
40

CASE 12


PRETREATMENT
BLOOD LEVELS
WHYTE
#180
AGE 36
CA. OF LUNG WITH
METASTASES TO
PECTORALIS NODE
SPINE
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
3,000 r
2,000 r
1,000 r
TBR 50r
2 OPPOSING 10 x 10 FIELDS TO
RT. LUNG MASS AND
ONE 7x10 TO LT. SHOULDER
DAYS
0
10
20
42

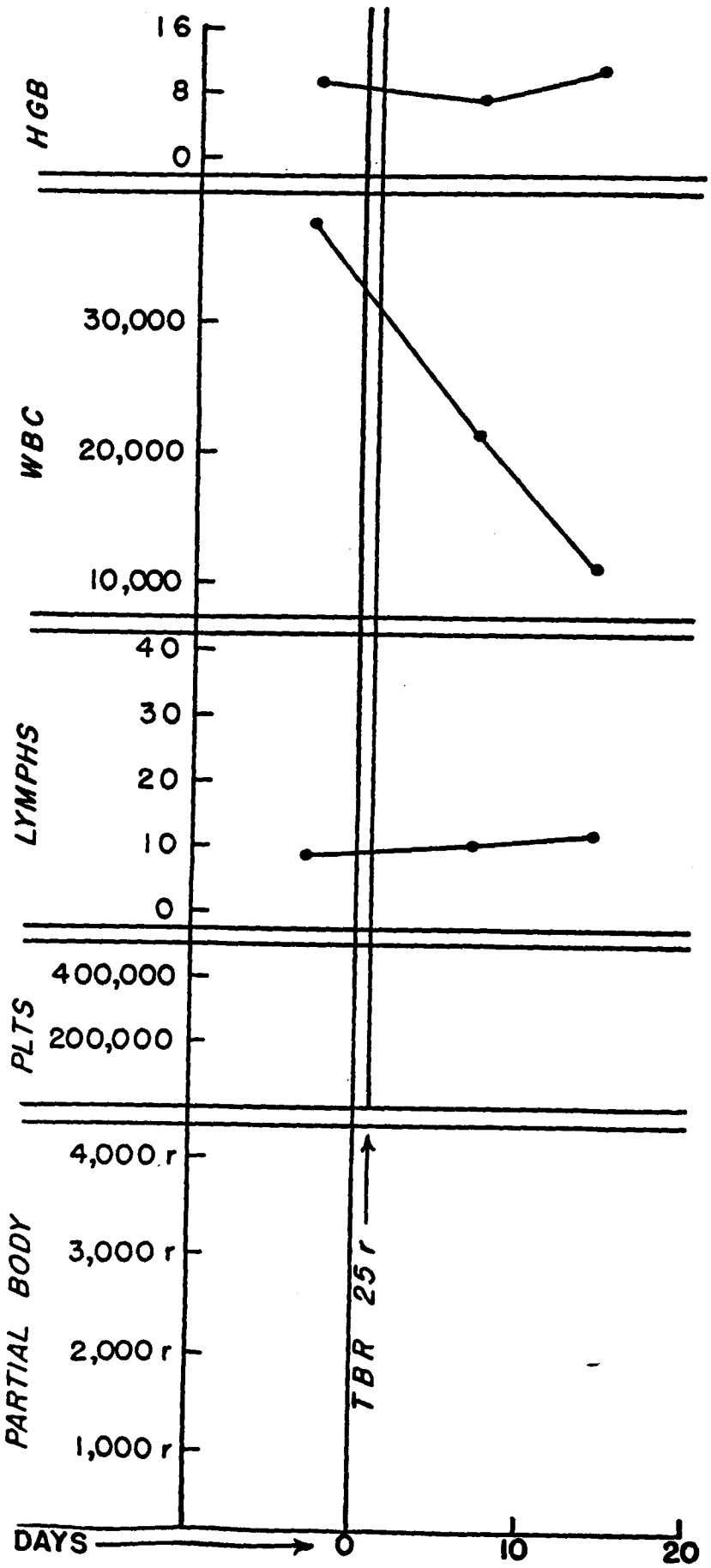
CASE 13

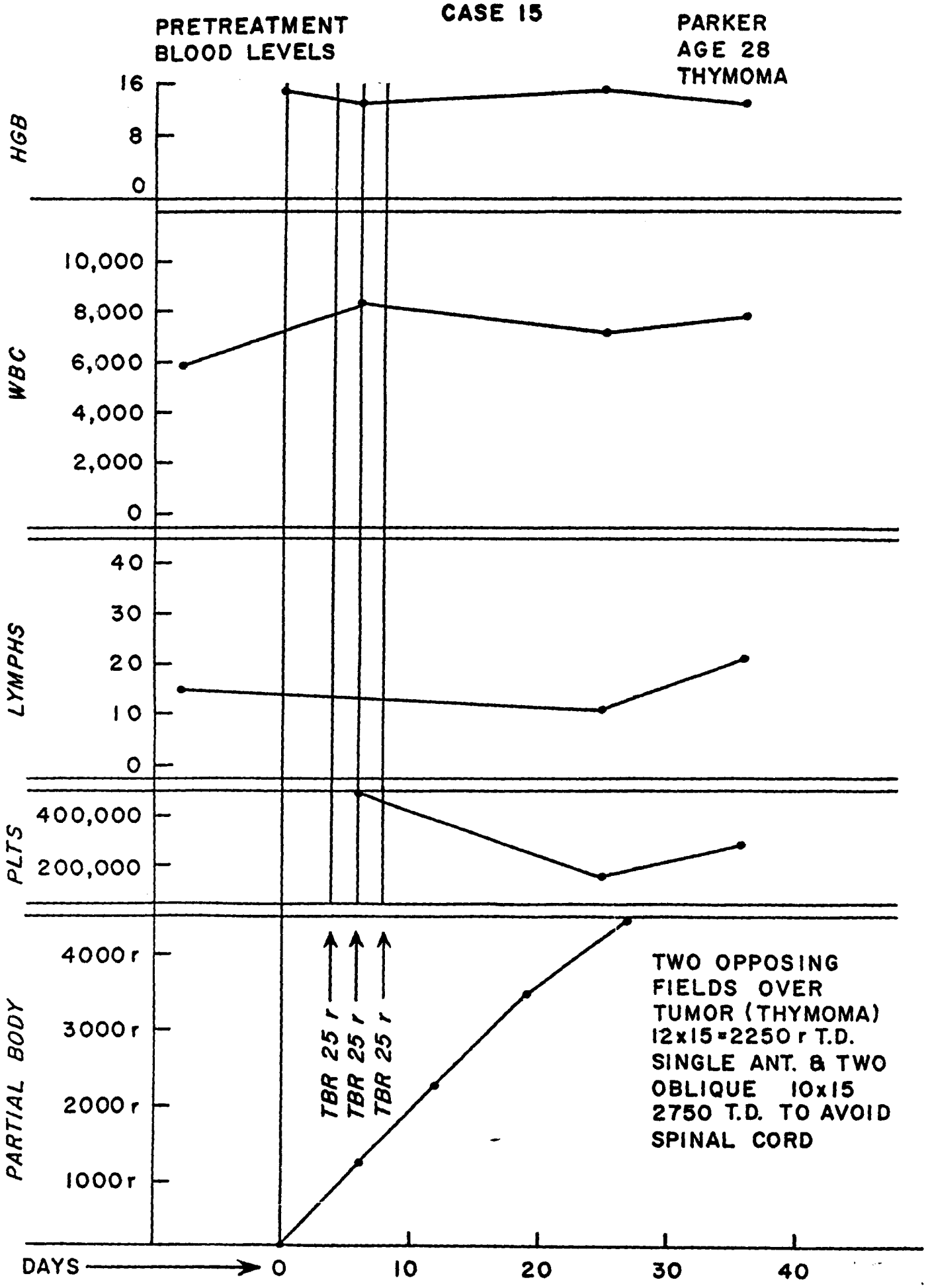

PRETREATMENT
BLOOD LEVELS
WOBBE #192
AGE 67
CA. RT. BUCCAL REGION
? MET. TO NODES
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPH.
40
30
20
10
0
PLTS
400,000
200,000
IRTIAL BODY
4000 r
3000 r
2000 r
1000 r
0
TBR 75 r
ONE 8x10 FLD. TO
RT. BUCCAL REGION
(EXTERNAL)
DAYS
0
10
20
30
40

CASE 14

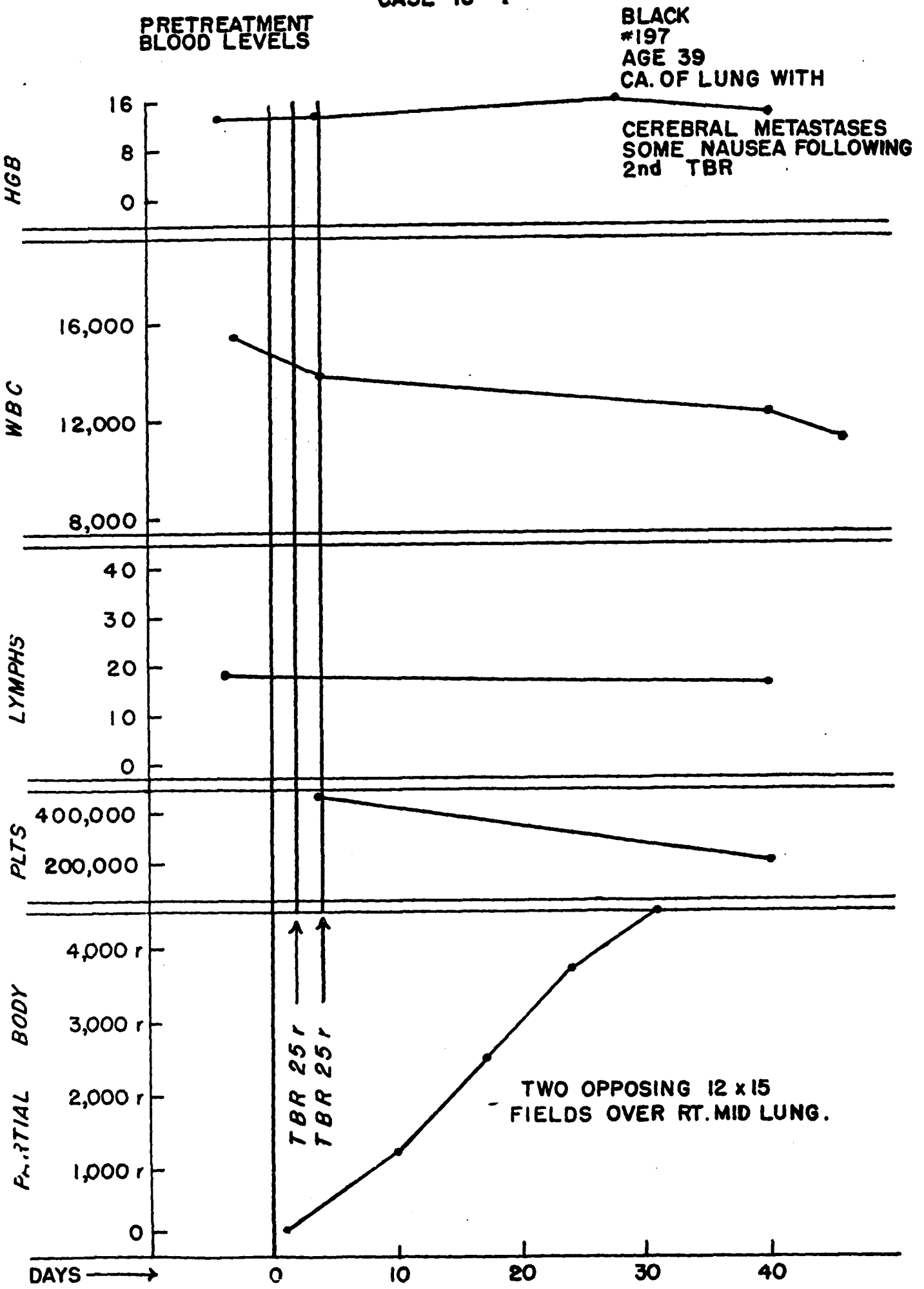
PRETREATMENT
BLOOD LEVEL

KOEPPEN #196
AGE 70
CHRONIC MYELOGENOUS
LEUKEMIA




CASE 15
PRETREATMENT BLOOD LEVELS
PARKER
AGE 28
THYMOMA
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
PARTIAL BODY
4000 r
3000 r
2000 r
1000 r
TBR 25 r
TBR 25 r
TBR 25 r
TWO OPPOSING FIELDS OVER TUMOR (THYMOMA) 12x15=2250 r T.D. SINGLE ANT. & TWO OBLIQUE 10x15 2750 T.D. TO AVOID SPINAL CORD
DAYS
0
10
20
30
40

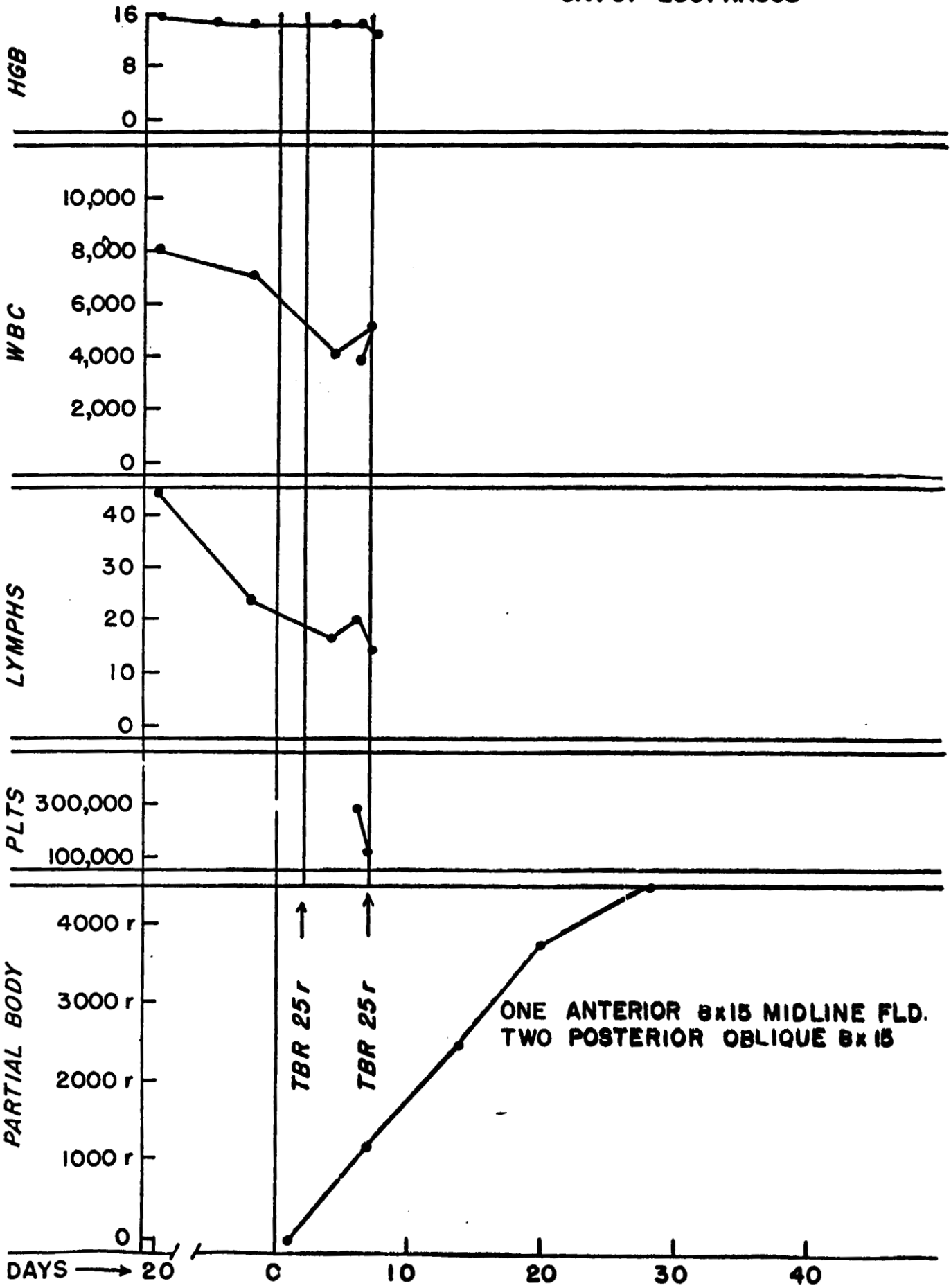
CASE 16


PRETREATMENT
BLOOD LEVELS
BLACK
#197
AGE 39
CA. OF LUNG WITH
CEREBRAL METASTASES
SOME NAUSEA FOLLOWING
2nd TBR
HGB
16
8
0
WBC
16,000
12,000
8,000
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
PARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
0
TBR 25 r
TBR 25 r
TWO OPPOSING 12 x 15
FIELDS OVER RT. MID LUNG.
DAYS
0
10
20
30
40

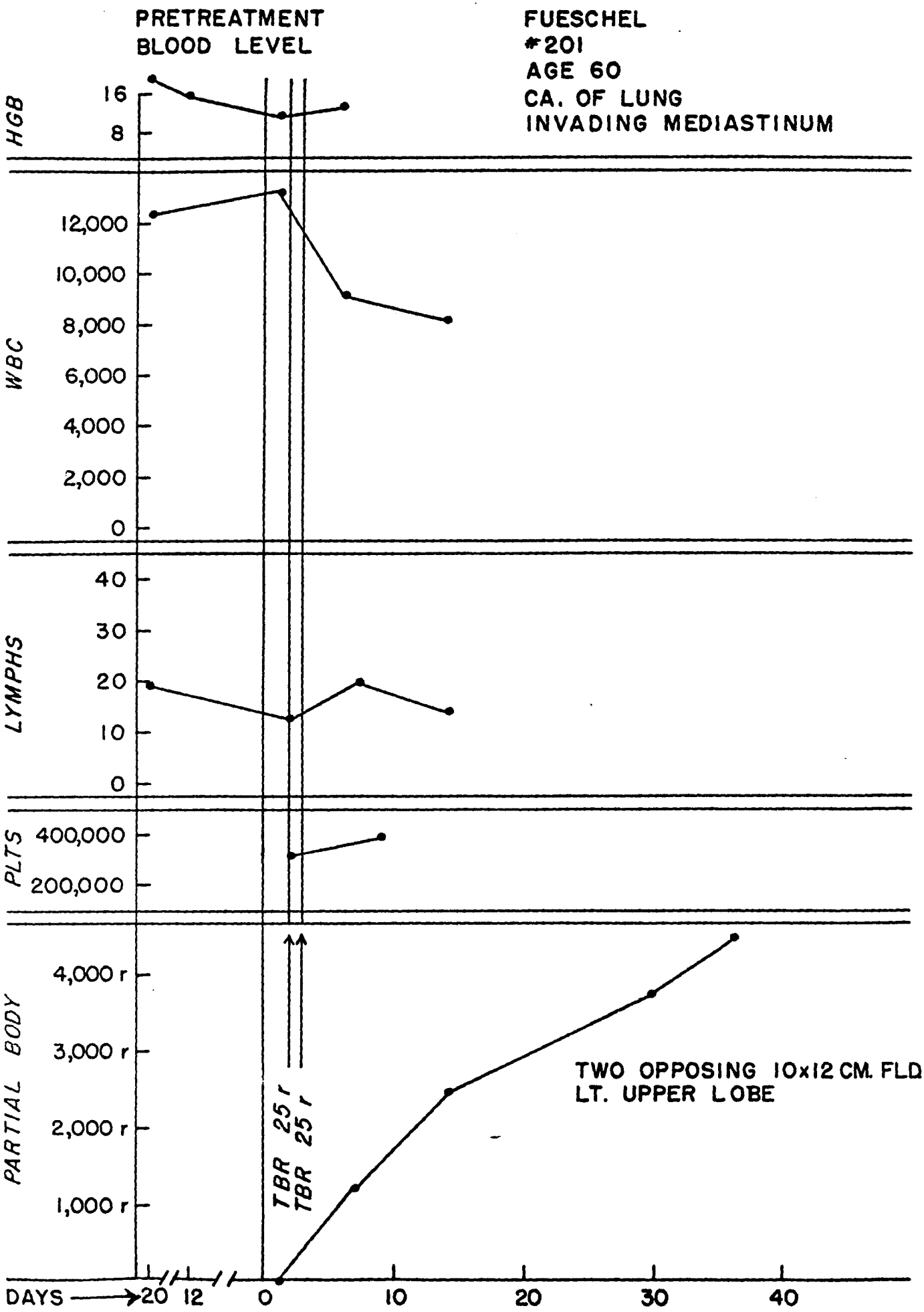
CASE 17

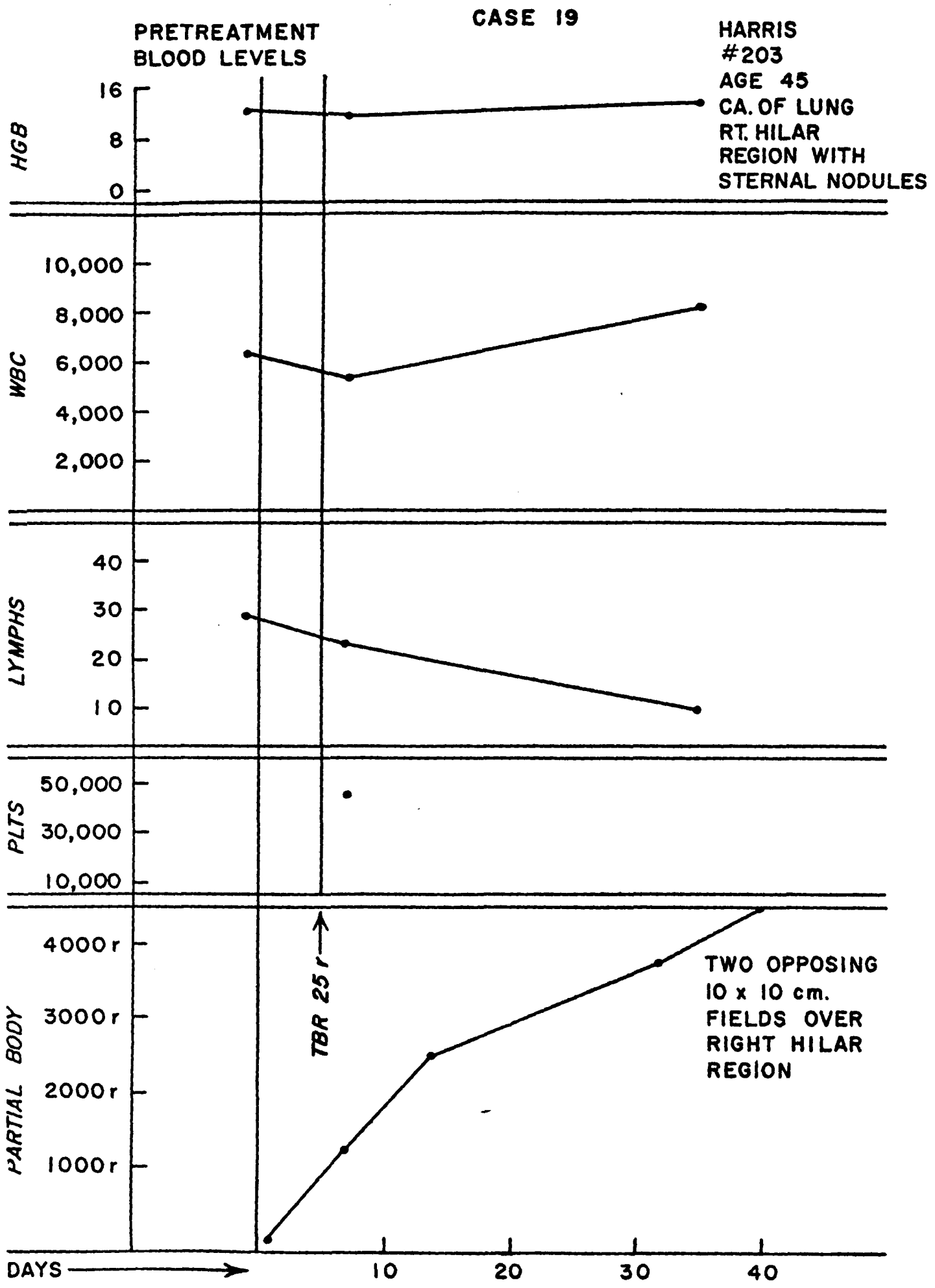
PRETREATMENT
BLOOD LEVELS

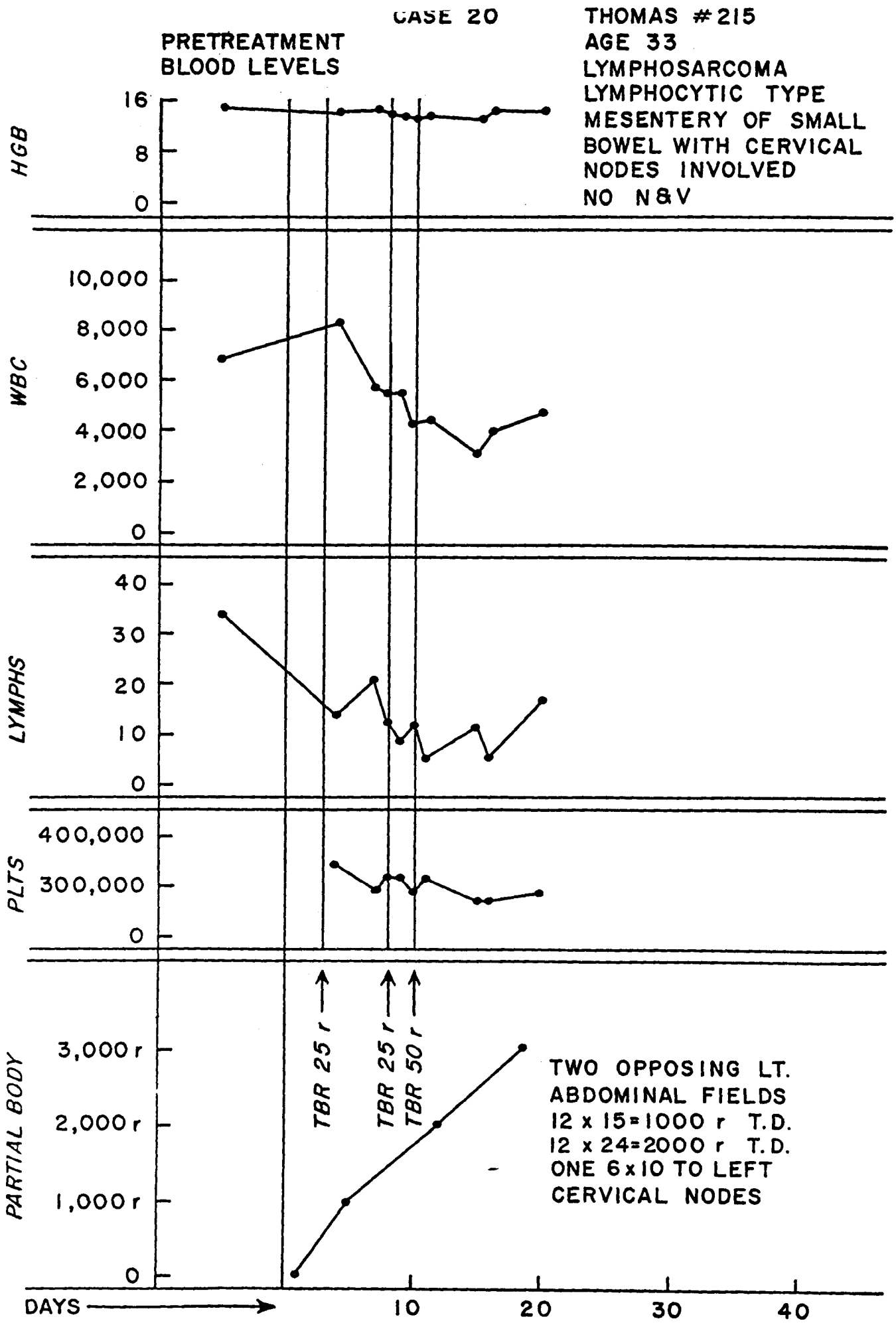
LADSON 199
AGE 65
CA. OF ESOPHAGUS



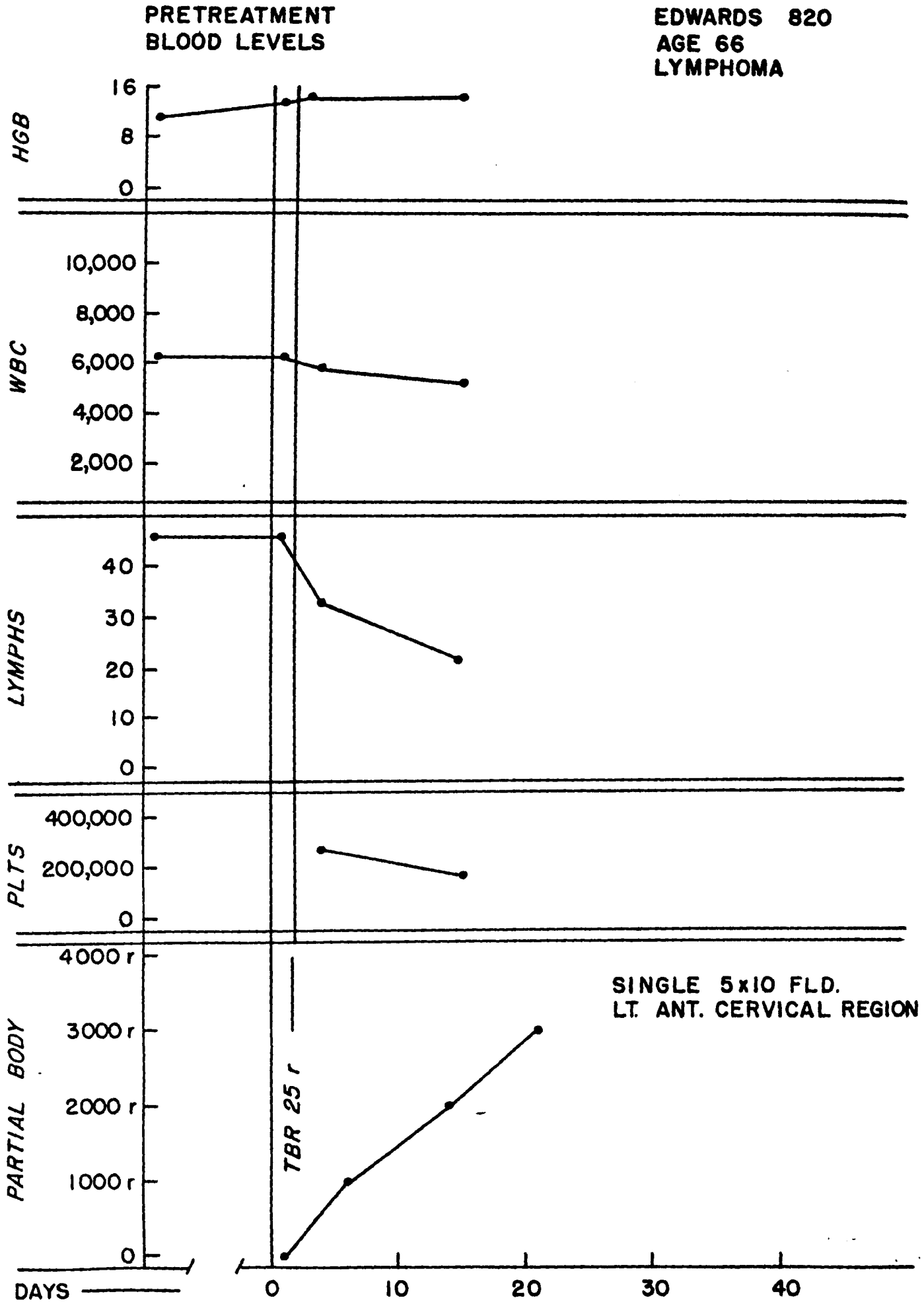
CASE 18


PRETREATMENT
BLOOD LEVEL
FUESCHEL
#201
AGE 60
CA. OF LUNG
INVADING MEDIASTINUM
HGB
16
8
WBC
12,000
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
PARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
TBR 25 r
TBR 25 r
TWO OPPOSING 10x12 CM. FLD
LT. UPPER LOBE
DAYS
20
12
0
10
20
30
40

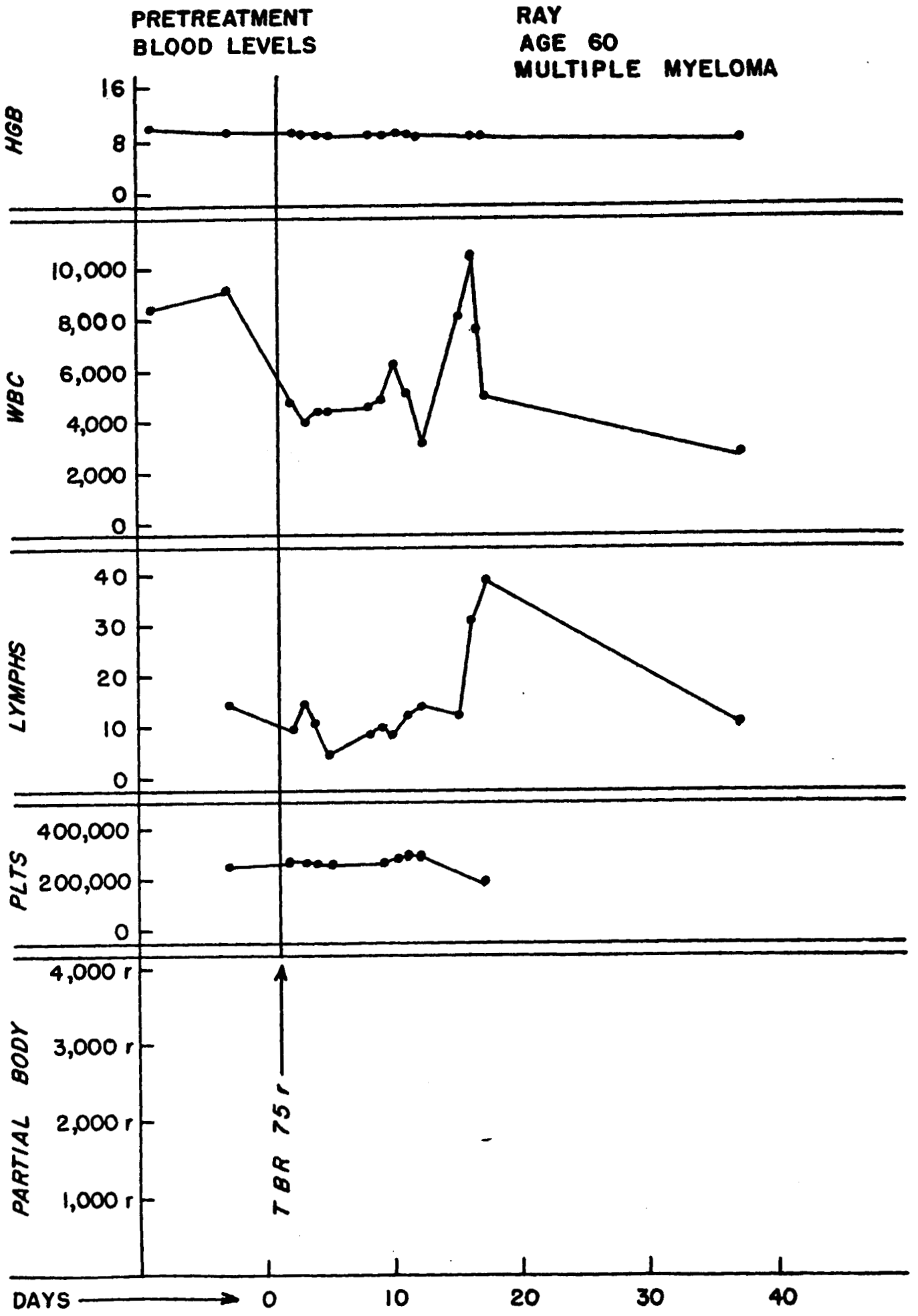

CASE 19
PRETREATMENT BLOOD LEVELS
HARRIS #203
AGE 45
CA. OF LUNG RT. HILAR REGION WITH STERNAL NODULES
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
LYMPHS
40
30
20
10
PLTS
50,000
30,000
10,000
PARTIAL BODY
4000 r
3000 r
2000 r
1000 r
TBR 25 r
TWO OPPOSING 10 x 10 cm. FIELDS OVER RIGHT HILAR REGION
DAYS
10
20
30
40


CASE 20
THOMAS #215
AGE 33
LYMPHOSARCOMA
LYMPHOCYTIC TYPE
MESENTERY OF SMALL
BOWEL WITH CERVICAL
NODES INVOLVED
NO N&V
PRETREATMENT
BLOOD LEVELS
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
300,000
0
PARTIAL BODY
3,000 r
2,000 r
1,000 r
0
TBR 25 r
TBR 25 r
TBR 50 r
TWO OPPOSING LT.
ABDOMINAL FIELDS
12 x 15=1000 r T.D.
12 x 24=2000 r T.D.
ONE 6x10 TO LEFT
CERVICAL NODES
DAYS
10
20
30
40

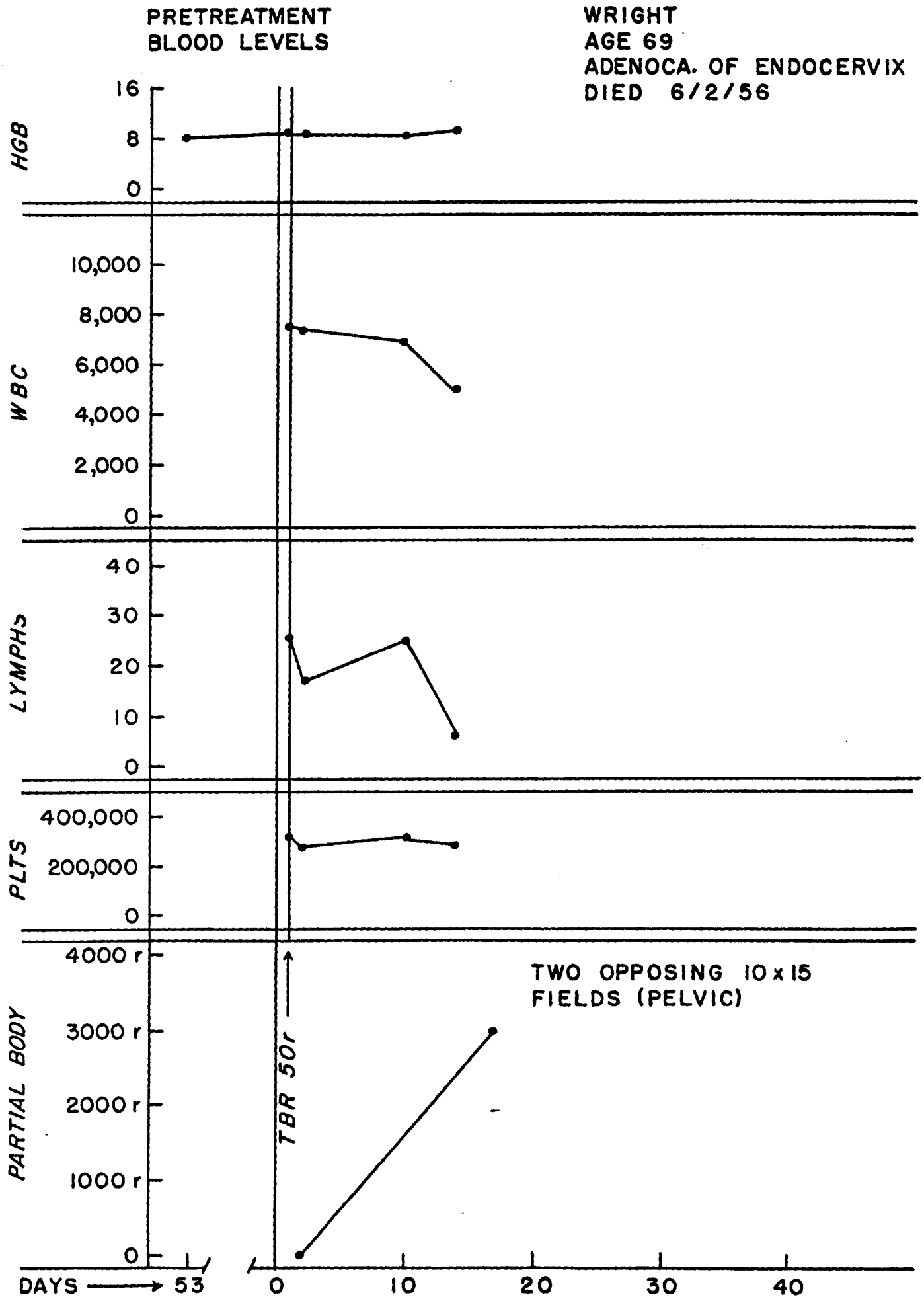
CASE 21


PRETREATMENT
BLOOD LEVELS
EDWARDS 820
AGE 66
LYMPHOMA
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
4000 r
3000 r
2000 r
1000 r
0
TBR 25 r
SINGLE 5x10 FLD.
LT. ANT. CERVICAL REGION
DAYS
0
10
20
30
40

CASE 22


PRETREATMENT
BLOOD LEVELS
RAY
AGE 60
MULTIPLE MYELOMA
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
4,000 r
3,000 r
2,000 r
1,000 r
T BR 75 r
DAYS
0
10
20
30
40

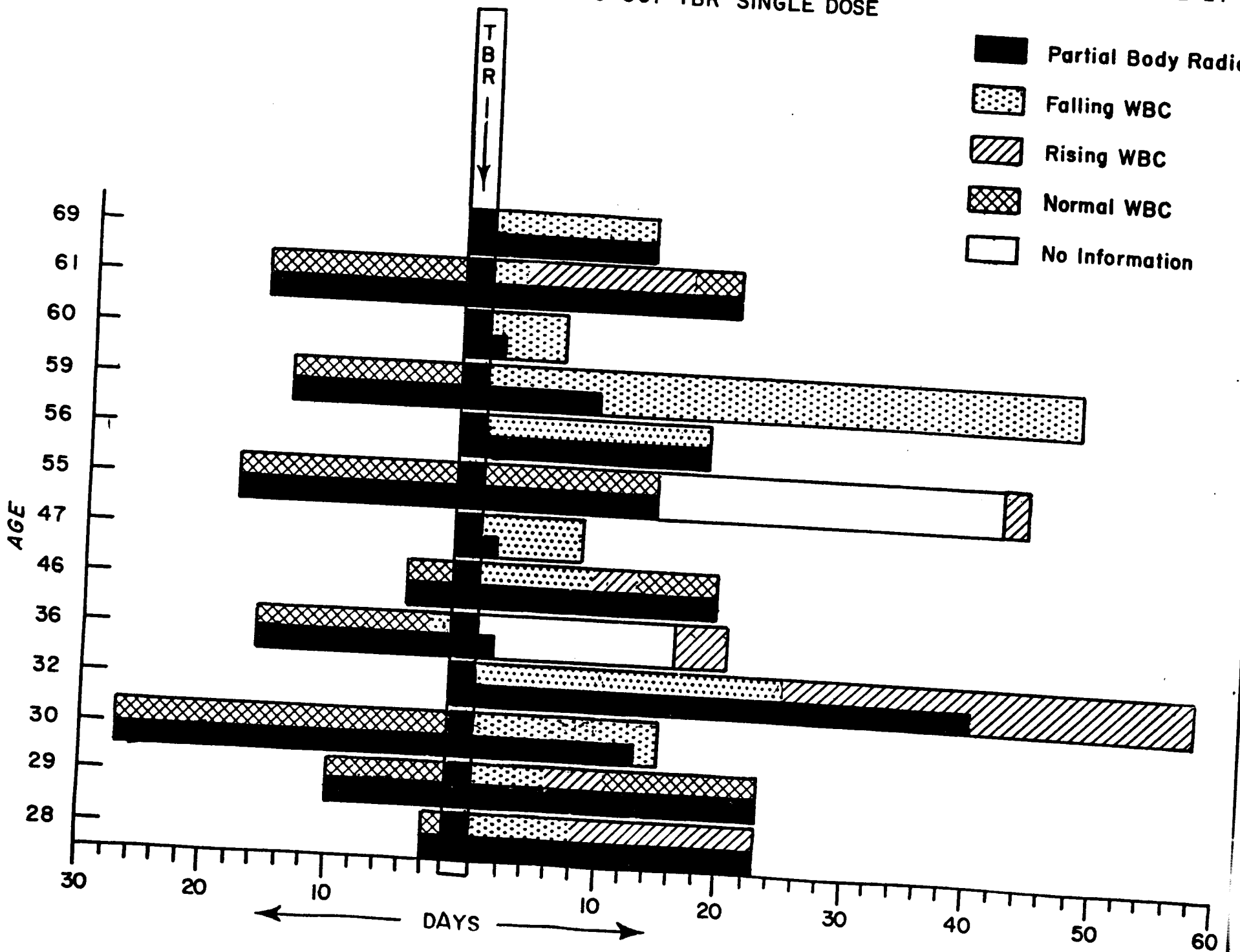
CASE 23


PRETREATMENT
BLOOD LEVELS
WRIGHT
AGE 69
ADENOCA. OF ENDOCERVIX
DIED 6/2/56
HGB
16
8
0
WBC
10,000
8,000
6,000
4,000
2,000
0
LYMPHS
40
30
20
10
0
PLTS
400,000
200,000
0
PARTIAL BODY
4000 r
3000 r
2000 r
1000 r
0
TBR 50r
TWO OPPOSING 10 x 15
FIELDS (PELVIC)
DAYS
53
0
10
20
30
40

AGE AND RESPONSE TO TBR

13 PATIENTS RECEIVING 50r TBR SINGLE DOSE

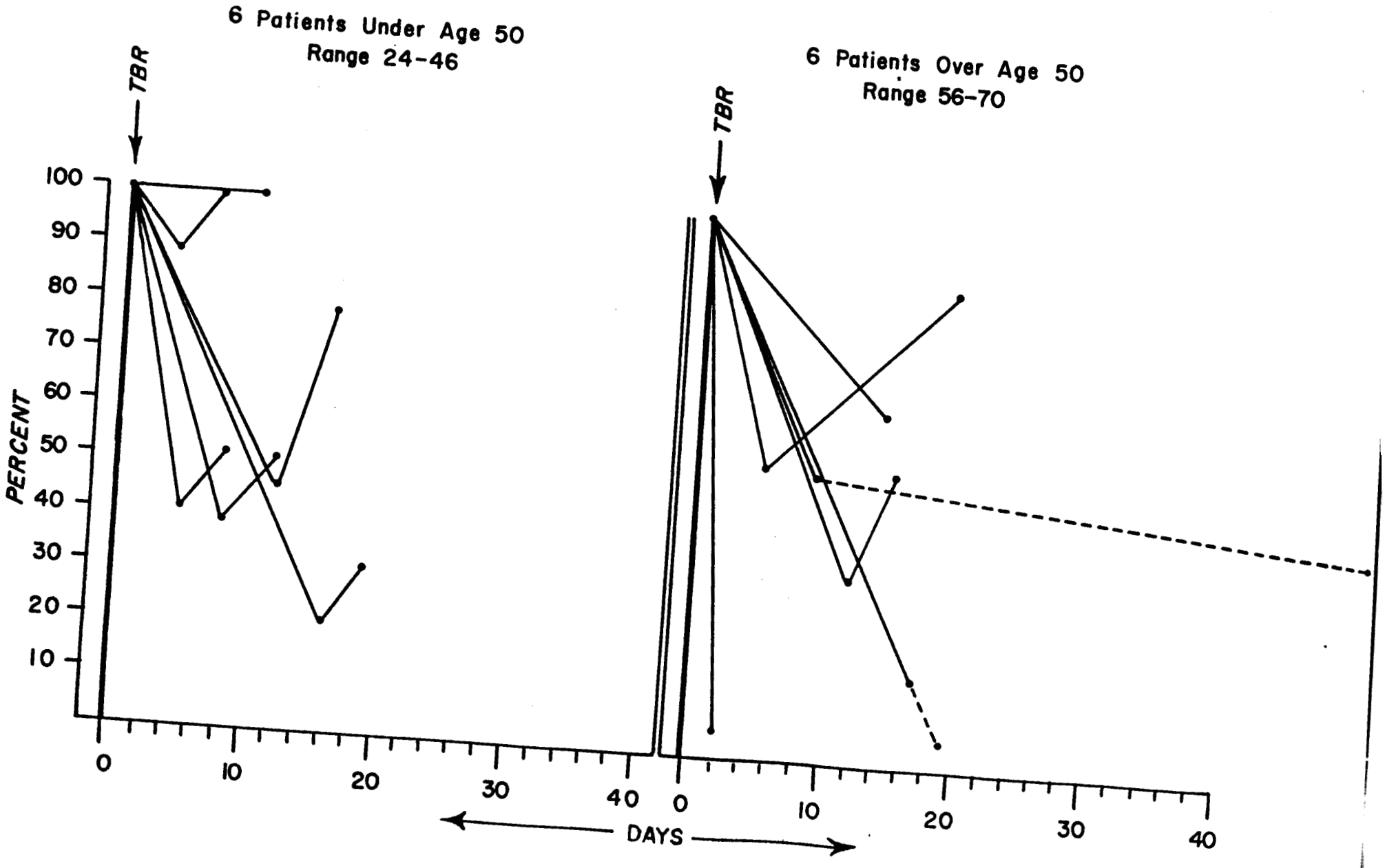
FIGURE 24



AGE AND RESPONSE TO TBR

PERIOD OF FALL AND BEGINNING RECOVERY OF WBC

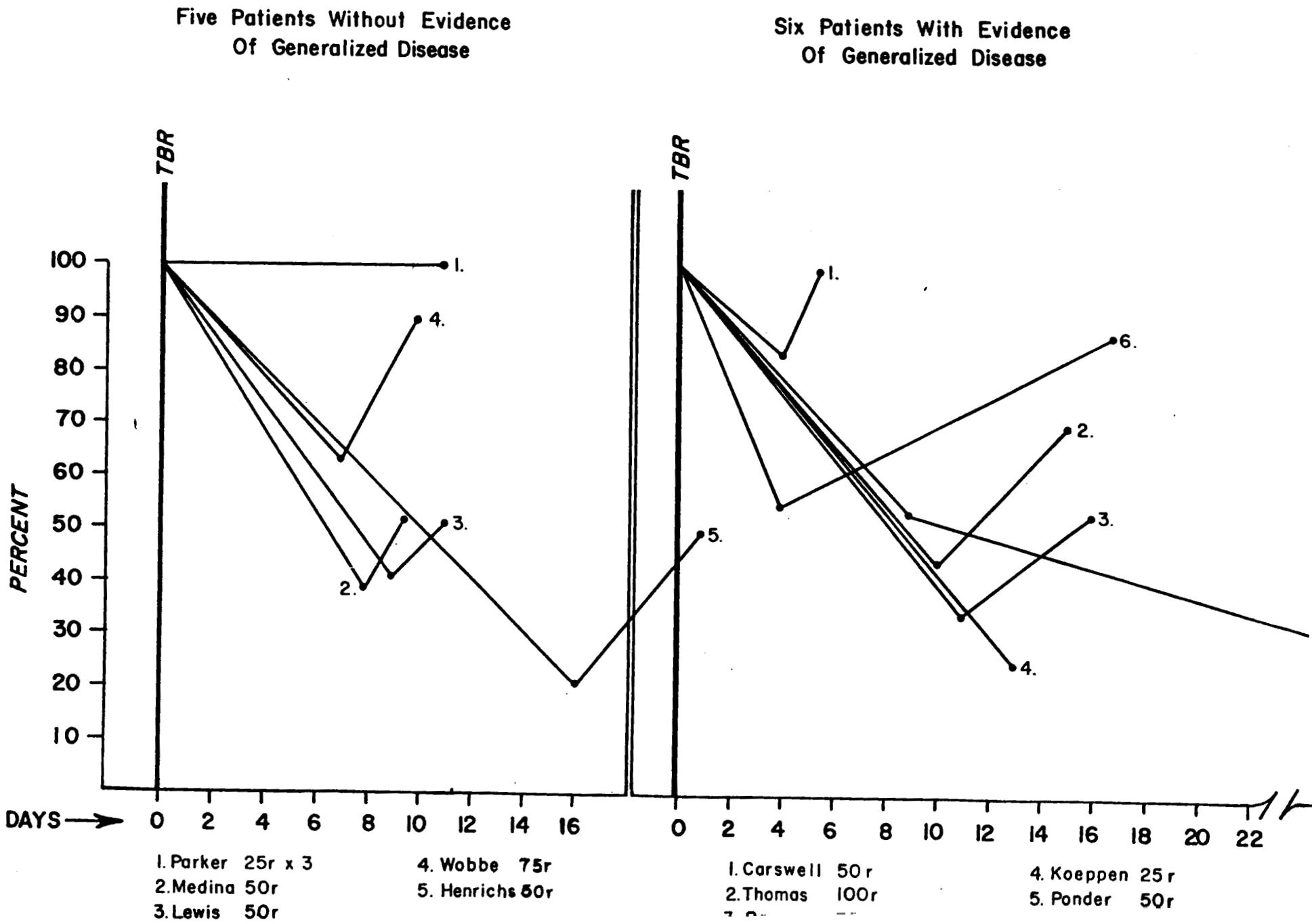
FIGURE 25



TBR

RESPONSE AND :TENT OF DISEASE

FIGURE 26



TBR

FIGURE 27

LEUCOCYTE RESPONSE IN 3 PATIENTS RECEIVING 25r TBR

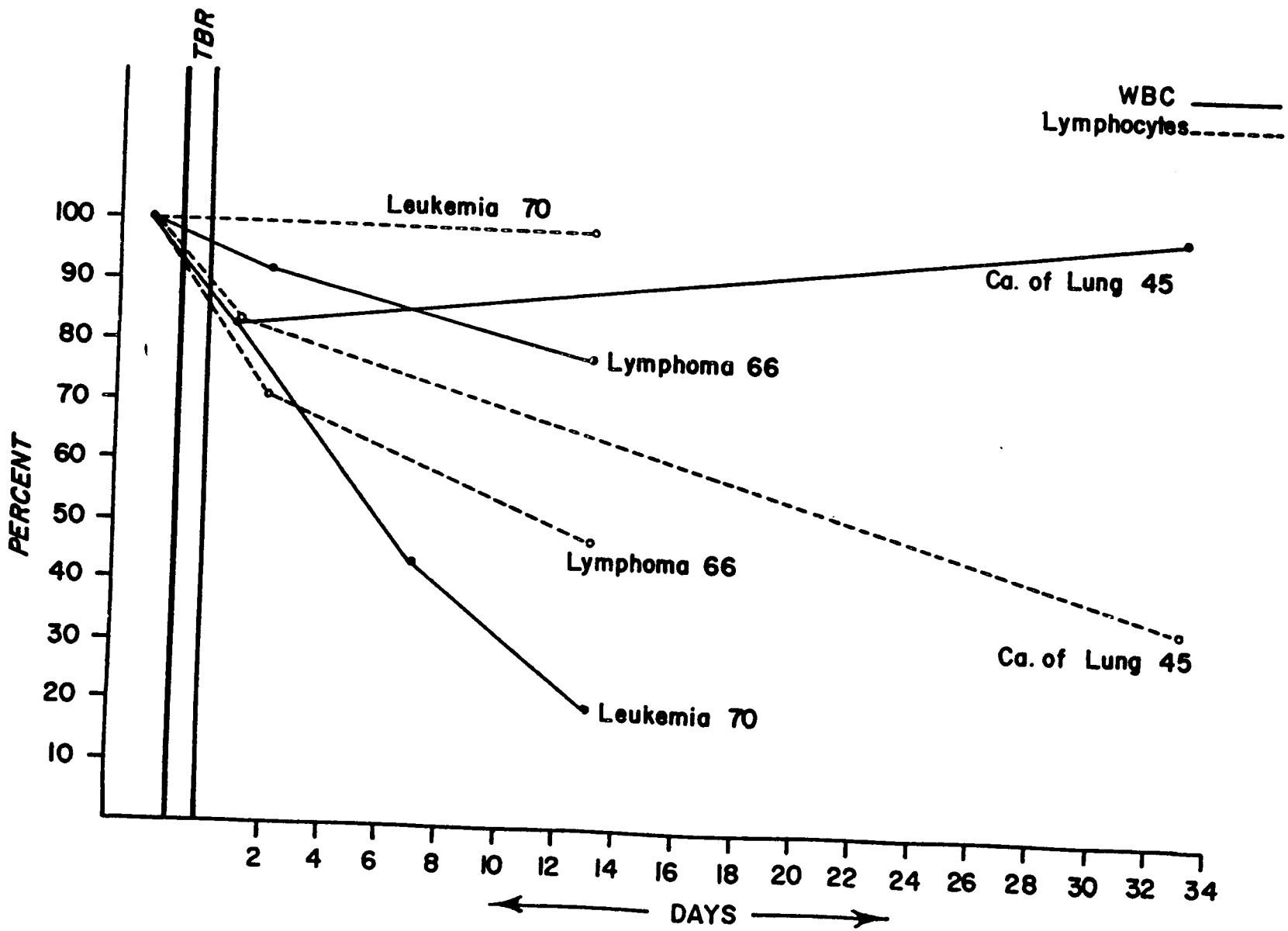


FIGURE 28

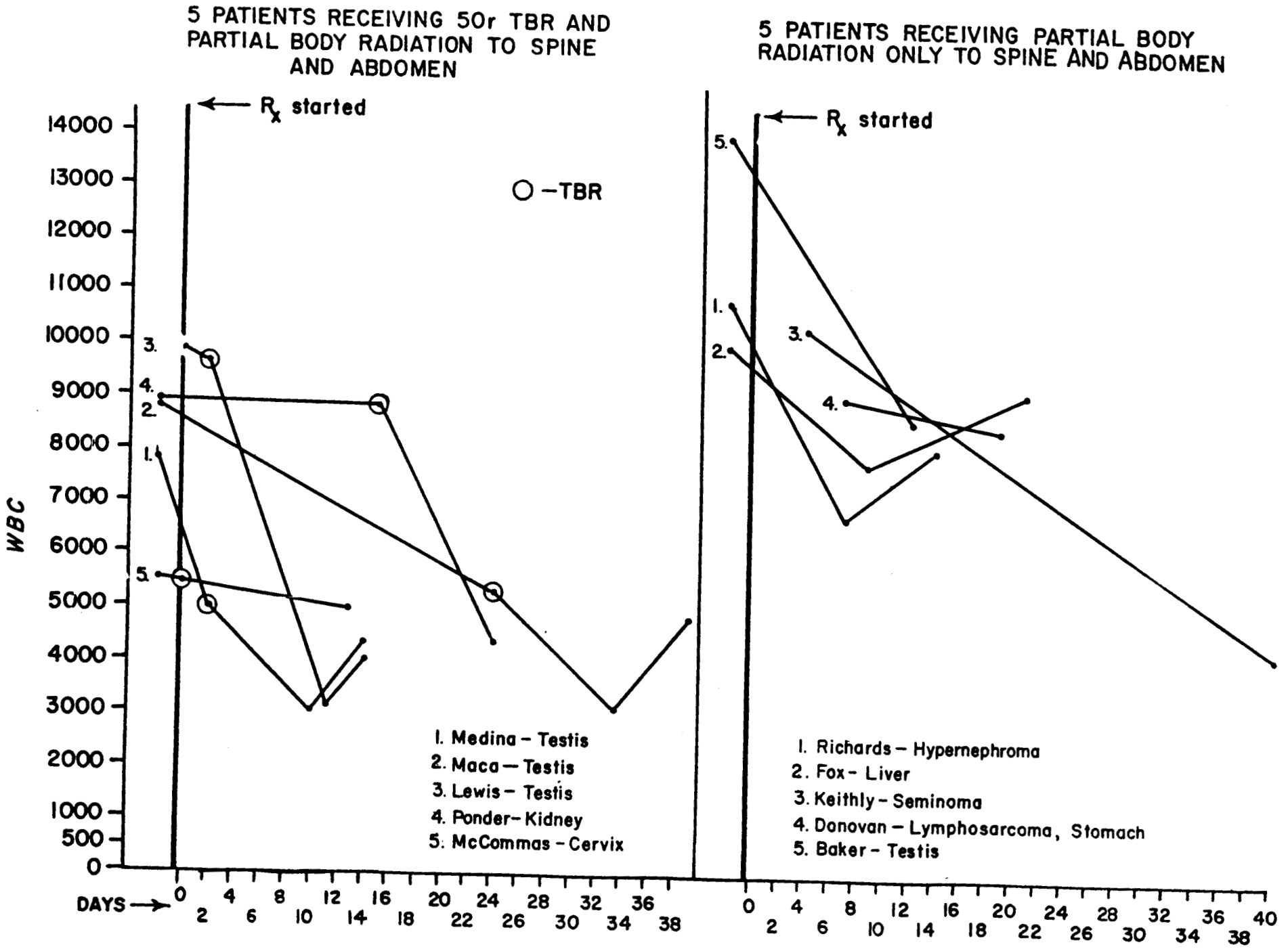

5 PATIENTS RECEIVING 50r TBR AND PARTIAL BODY RADIATION TO SPINE AND ABDOMEN
5 PATIENTS RECEIVING PARTIAL BODY RADIATION ONLY TO SPINE AND ABDOMEN
Rx started
O –TBR
WBC
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
0
DAYS
1. Medina – Testis
2. Maca – Testis
3. Lewis – Testis
4. Ponder – Kidney
5. McCommas – Cervix
1. Richards – Hypernephroma
2. Fox – Liver
3. Keithly – Seminoma
4. Donovan – Lymphosarcoma, Stomach
5. Baker – Testis

FIGURE 29

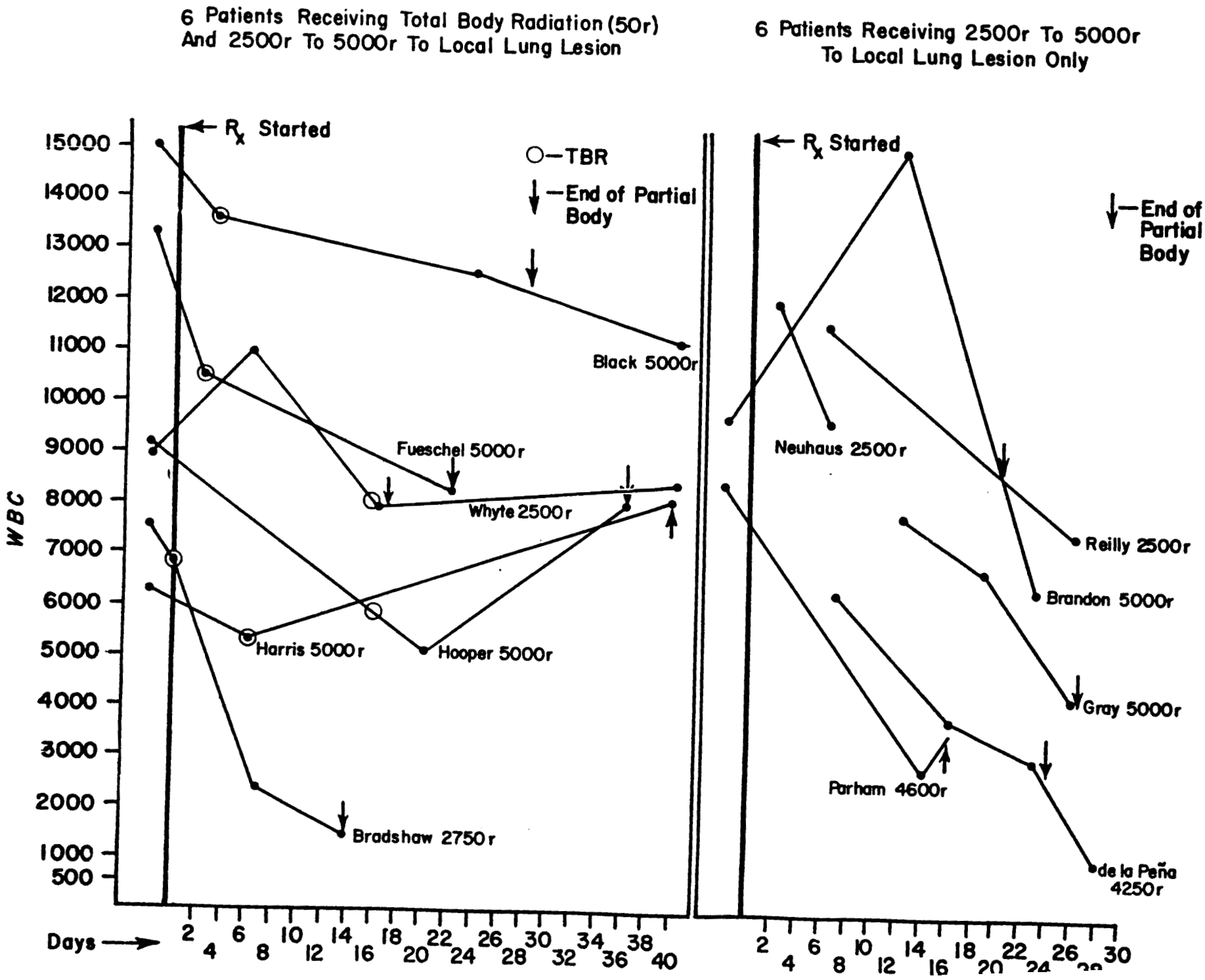

6 Patients Receiving Total Body Radiation (50r) And 2500r To 5000r To Local Lung Lesion
6 Patients Receiving 2500r To 5000r To Local Lung Lesion Only
Rx Started
O—TBR
—End of Partial Body
WBC
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
Days
Black 5000r
Fueschel 5000r
Whyte 2500r
Harris 5000r
Hooper 5000r
Bradshaw 2750r
Neuhaus 2500r
Reilly 2500r
Brandon 5000r
Gray 5000r
Parham 4600r
de la Peña 4250r

FIGURE 30 B

COMPARISON OF WBC RESPONSE TO TOTAL BODY RADIATION GIVEN BY STATIONARY FIELDS AND BY ROTATION

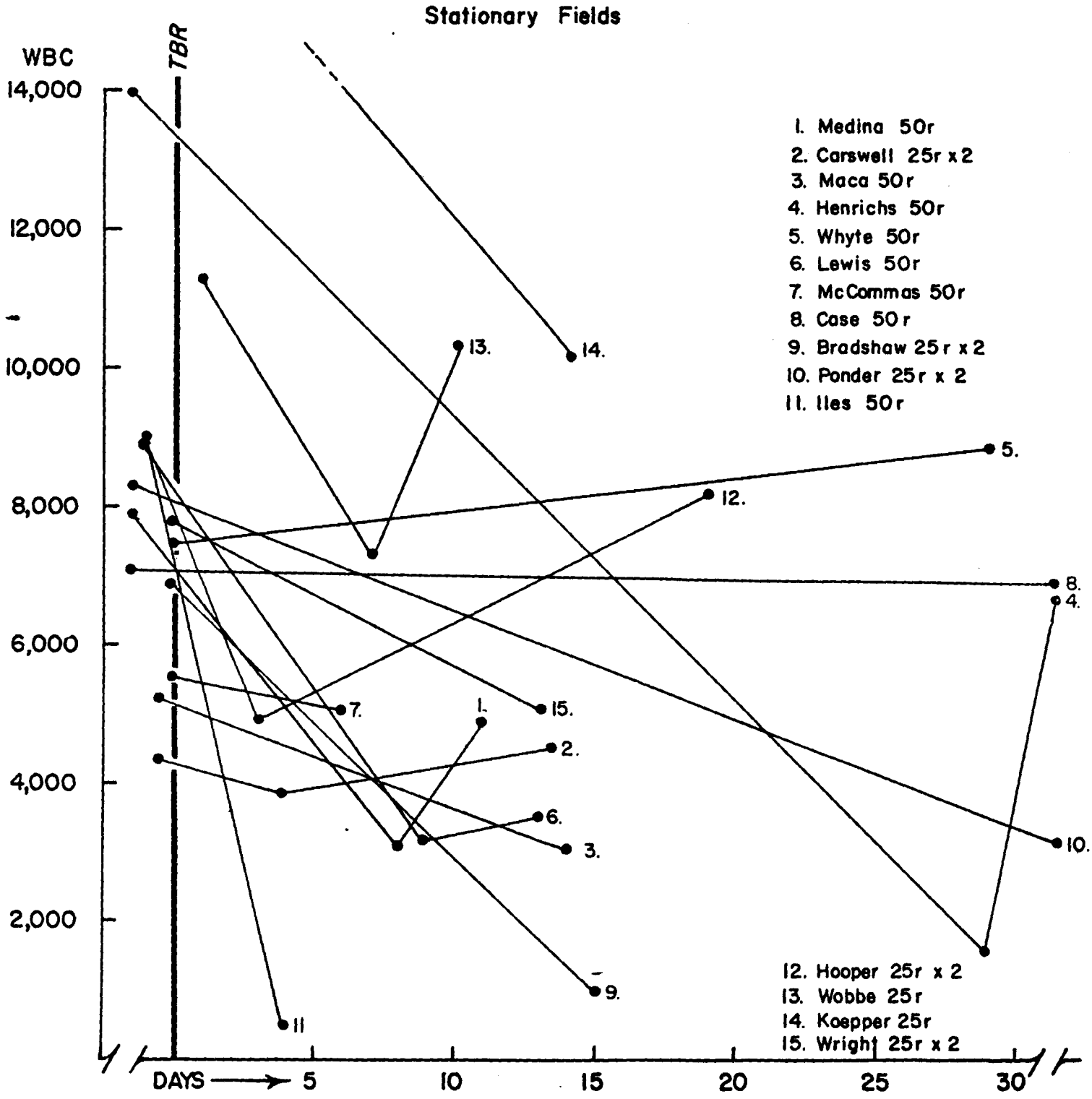
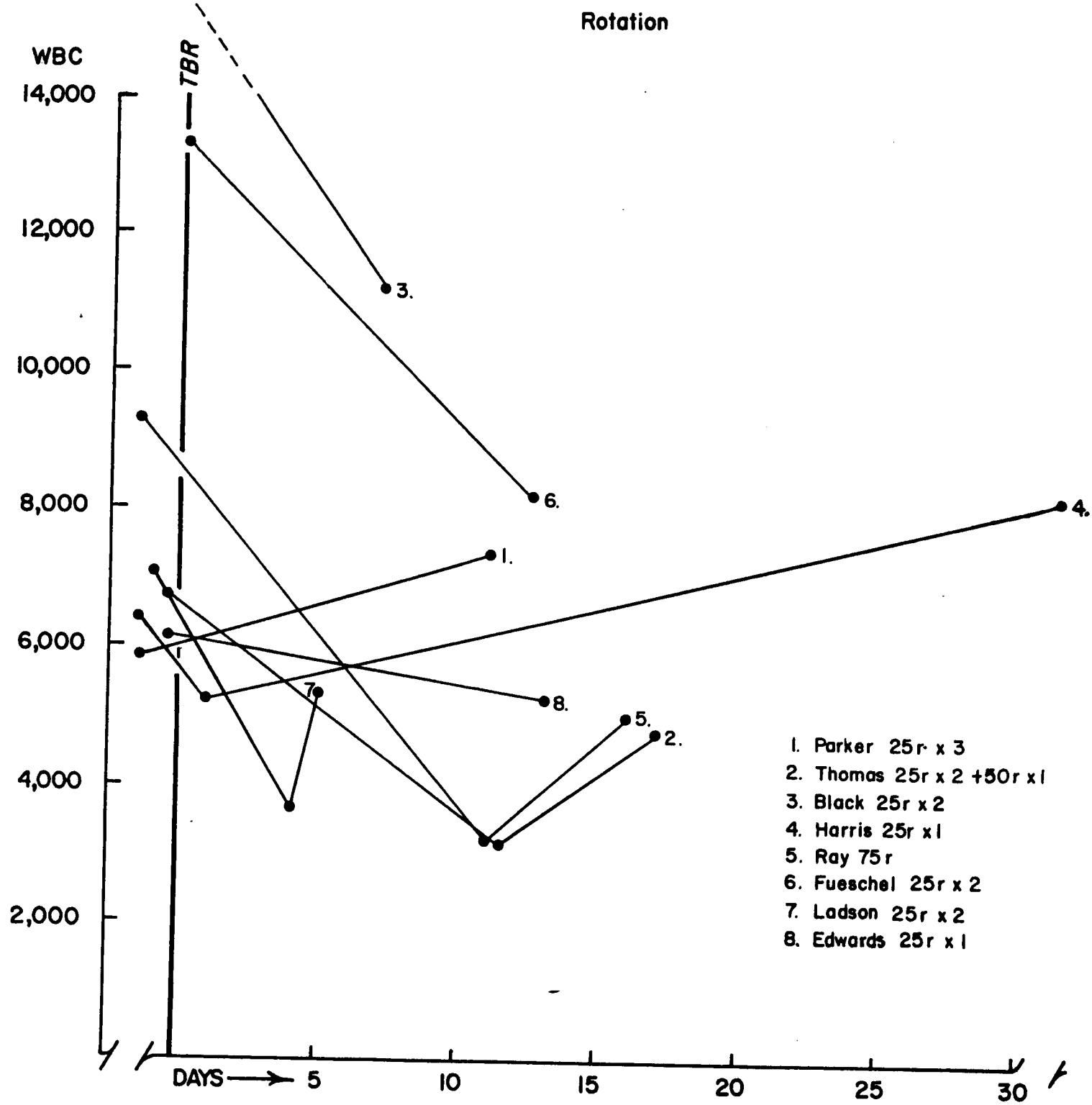


FIGURE 30 A

COMPARISON OF WBC RESPONSE TO TOTAL BODY RADIATION GIVEN BY STATIONARY FIELDS AND BY ROTATION



THE THERAPEUTIC USE OF SINGLE DOSES OF TOTAL BODY RADIATION

BY

VINCENT P. COLLINS, M.D., AND R. KENNETH LOEFFLER, M.D.

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THE THERAPEUTIC USE OF SINGLE DOSES OF TOTAL BODY RADIATION*†

By VINCENT P. COLLINS, M.D., *and* R. KENNETH LOEFFLER, M.D.
HOUSTON, TEXAS

RADIATION therapy and chemotherapy are recognized as having equivalent or complementary roles in the treatment of certain types of cancer. In general, radiation has been restricted to the treatment of relatively localized manifestations, and chemotherapy has been used when the disease is more widely disseminated. There has been limited use of total body irradiation in the treatment of generalized neoplastic disease. In the Heublein technique[8,11] low intensity, continuous irradiation was used to administer doses up to 450 roentgens in three weeks. Hempelmann *et al.*,[6] writing on the acute radiation syndrome, noted that 100 r of 200 kv. roentgen rays could be delivered to the entire body of the patient without causing symptoms of any sort. Recently, Osgood and Seaman[12] have advocated a "titration technique" in the treatment of leukemia in which doses of 10–25 r were given to the whole body at regularly spaced intervals. In a scrupulous effort to avoid radiation sickness and bone marrow depression, a conventional technique employing total body irradiation for the treatment of polycythemia utilizes doses of 25 r repeated to a total of 300 r in three weeks. From these different techniques, using varying formulae of intensity, dose, and time, it is difficult to assess the tolerance to whole body irradiation.

Perhaps the most extensively employed chemotherapeutic agent has been nitrogen mustard, methyl bis (beta chloroethyl) amine (HN_2). This agent has been used in almost every form of malignant disease and in some benign conditions such as rheumatoid arthritis.[4] It has become the standard form of therapy for generalized Hodgkin's disease. In accepted clinical doses, nitrogen mustard produces a sharp systemic reaction and the patient is heavily sedated before treatment to control nausea and vomiting. Hematopoietic depression is constant, and severe leukopenia and thrombocytopenia is a recognized hazard of repeated courses. These toxic side effects have not been a deterrent to common use although they exceed the severity of radiation sickness.

In 1950 Gellhorn and Collins[5] undertook a comparative study of two groups of patients with Hodgkin's disease, one of which had received radiation and nitrogen mustard in alternating therapeutic courses, and the other radiation therapy alone. It could not be shown that the addition of nitrogen mustard to the therapy regimen increased survival time but the drug was regarded as a useful adjunct to the extent that it reduced the time under treatment and the amount of radiation required. If nitrogen mustard did not increase survival time beyond that obtained with radiation therapy alone, its only purpose was to offer the convenience of a systemic approach to treatment. It seemed possible that higher doses of total body irradiation might offer equal benefit with side effects of less severity. Phillips *et al.*[13] had studied the application of massive doses of radiation to liver for metastatic disease. Court Brown[3] had reported observations on symptoms associated with single therapeutic doses of roentgen radiation to large portions of the body, and to the whole body.

In a previous report the tolerance to total body irradiation was compared with the effects of nitrogen mustard and triethylene

* From the Department of Radiology, Baylor University College of Medicine, and the Jefferson Davis Hospital, Houston, Texas.
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melamine.[10] Total body irradiation in single doses up to 150 r was less depressing for hematopoiesis and patients were free of malaise that was constantly associated with these drugs. These observations suggested that a therapeutic effect of total body irradiation might be sought in patients having disseminated disease ordinarily treated by a variety of chemotherapeutic agents.

In the present series of patients, dose has been expressed in roentgens on skin and measurements were made with a Victoreen chamber on the surface of a pressdwood phantom at treatment distance. Court Brown and Mahler[2] reported their series of single exposures to radiation in terms of energy absorbed or integral dose. There was some necessity for this in that their patients received treatment to varying portions and proportions of the body, and dose in roentgens would have no direct correlation with tolerance of the individual to radiation. For purposes of duplication, dose on skin represents the simplest expression of exposure to radiation. Boden and Cohen[1] have called attention to variations that exist in measuring dose in different institutions and it appears that no accuracy would be gained in the assumptions and calculations necessary for determining integral dose for total body irradiation.

In addition to the usual blood examinations, radioactive iron tracer studies were carried out because of the work of Hennessy and Huff[7,9] indicating a quantitative relation between the utilization of injected iron for hemoglobin production, and dose of total body irradiation, in rats. The half time of disappearance of radioiron from the blood is normally one to two hours for humans. Prolongation of the half time indicates decreased hemoglobin formation and may be useful as an early and sensitive index of change in guiding further therapy.

	Initial	*Low*	*Final (11 mo.)*
Hb.	11.9 gm.	7.6 gm. @ 5 wk.	11.0 gm.
R.B.C.	4,300,000	1,700,000 @ 5 wk.	3,800,000
W.B.C.	29,000	4,000 @ 8 wk.	10,000
Platelets	240,000	110,000 @ 8 wk.	148,000
Iron turnover half time	1.3 hr.	4.2 hr. @ 23 days	0.4 hr.

REPORT OF CASES

Case I. B.L. (AR-8422) A male, aged seventy-three, developed generalized lymphadenopathy in November, 1951, and a diagnosis of "lymphoma" was made by biopsy. Treatment was withheld because of lack of symptoms. In March, 1953, the patient was admitted to the hospital because of 20 pounds weight loss, pain in left shoulder, and edema of left upper extremity. There was extensive lymphadenopathy with nodes as large as 5 cm. in diameter; liver extended 5 cm. below the costal margin.

On March 23, 1953, the patient received 75 r (skin dose) total body irradiation anteriorly and 75 r posteriorly (250 kv., constant potential, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). In the first forty-eight hours the patient was anorexic but there was no nausea, vomiting or diarrhea. On the third day the patient's appetite returned and the lymph nodes began to diminish in size. On May 12, 1953, he was discharged from the hospital and returned to work. Later in the month he received 600 r tissue dose to the mediastinum in eight days on an out-patient basis. In December, 1953, in another city, he underwent partial gastric resection for ulcer of the lesser curvature. At present he is convalescing satisfactorily.

Laboratory data during the period associated with total body irradiation were as follows:

Differential white cell count became normal at eight weeks.

Case II. W.D. (AJ-6024) A seventy-two year old white male was admitted for repair of inguinal hernia and was discovered to have a white blood cell count of 155,000. The differential white cell count was consistent with chronic myelogenous leukemia. Liver and spleen were palpably enlarged. The blood pressure was 200/90. He had lost 20 pounds in

weight in the past year. On June 24, 1953, he received 150 r (skin dose) total body irradiation to the anterior aspect of body (250 kv., half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild anorexia on the following morning but his appetite was normal by noon. There was no nausea, vomiting or malaise. Liver and spleen gradually diminished in size and were no longer palpable after two weeks.

Laboratory data during treatment and follow-up were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	10.1 gm.	7.5 gm. @ 4 wk.	11.0 gm.
R.B.C.	3,800,000	2,900,000 @ 4 wk.	3,100,000
W.B.C.	193,000	11,000 @ 3 mo.	98,000
Platelets	265,000	225,000 @ 1 wk.	216,000
Iron turnover half time	0.6 hr.	2 hrs. @ 1 day	1.5 hr.

Differential white cell count became normal at three months.

Case III. J.B.C. (AX-7573) A fifty-one year old white male was admitted to the hospital on September 10, 1953, with a biopsy diagnosis of multiple myeloma. He had been paraplegic and incontinent of urine and feces for three weeks; he had developed a large sacral decubitus ulcer, his general condition was poor and he complained of severe dorsal and lumbar back pain. He was placed on a Foster frame and daily care was given to the decubitus ulcer, which showed slow improvement.

On September 15 he was given 200 r (skin dose) total body irradiation (250 kv., peak, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild nausea of one day's duration; there was no vomiting. Because there was only partial loss of tactile sensation accompanying the motor paralysis, the total body irradiation was followed two weeks later by local roentgen therapy to the spine. A tissue dose of 675 r was delivered in ten days to vertebral bodies from C-4 to S-1. No change was detected in the neurologic findings; however, narcotic requirements for pain were considerably less than before treatment. The patient's condition gradually deteriorated and he died on Oct. 28, 1953. No autopsy was obtained.

Laboratory data during the period associated with total body irradiation were as follows:

	Initial	*Low*	*Final (6 wk.)*
Hb.	11.0 gm.	5.7 gm. @ 4 wk.	7.5 gm.
W.B.C.	8,500	4,050 @ 5 wk.	5,500
Platelets	240,000	220,000 @ 4 wk.	250,000

There was no change in differential white blood cell count.

Case IV. O.B. (Y-13361) This white female, aged fifty-eight, gave a six year history of backache radiating to the legs. In April, 1948, she received roentgen therapy to a destructive lesion in the body of the second lumbar vertebra with diminution of pain. In 1951 a second course of therapy was given to this area, and in January, 1952, a third course. On Feb. 23, 1952, a spinal fusion was carried out and a diagnosis of multiple myeloma was established. Further lesions developed in skull and ribs. On Oct. 26, 1953, the patient, now a paraplegic with complete destruction of the body of the third lumbar vertebra, and constant severe back pain, was transferred from another hospital for total body irradiation. On Nov. 11, 1953, with patient turned on her side in bed, she received 200 r (skin dose) to back (250 kv., half-value layer 1.8 mm. Cu, target skin distance 365 cm). There were two episodes of vomiting without nausea at four and six hours after treatment and minimal nausea but no further vomiting on the first and second post-treatment days. From the third treatment day there were no further symptoms of nausea and moderate pain relief was noted. Pain began to become more severe again after five weeks. On Dec. 16, 1953 (five weeks) the patient received another 100 r (skin dose) to the back under the same conditions as previously. There were no symptoms of nausea or vomiting, and again there was some reduction in back and leg pain. Pain was relieved for about one month and then recurred with the same severity as before treatment. For this reason a cervical cordotomy was planned, but the patient died at operation on Jan. 28, 1954.

An autopsy was performed. The tumor that had received intensive local irradiation showed

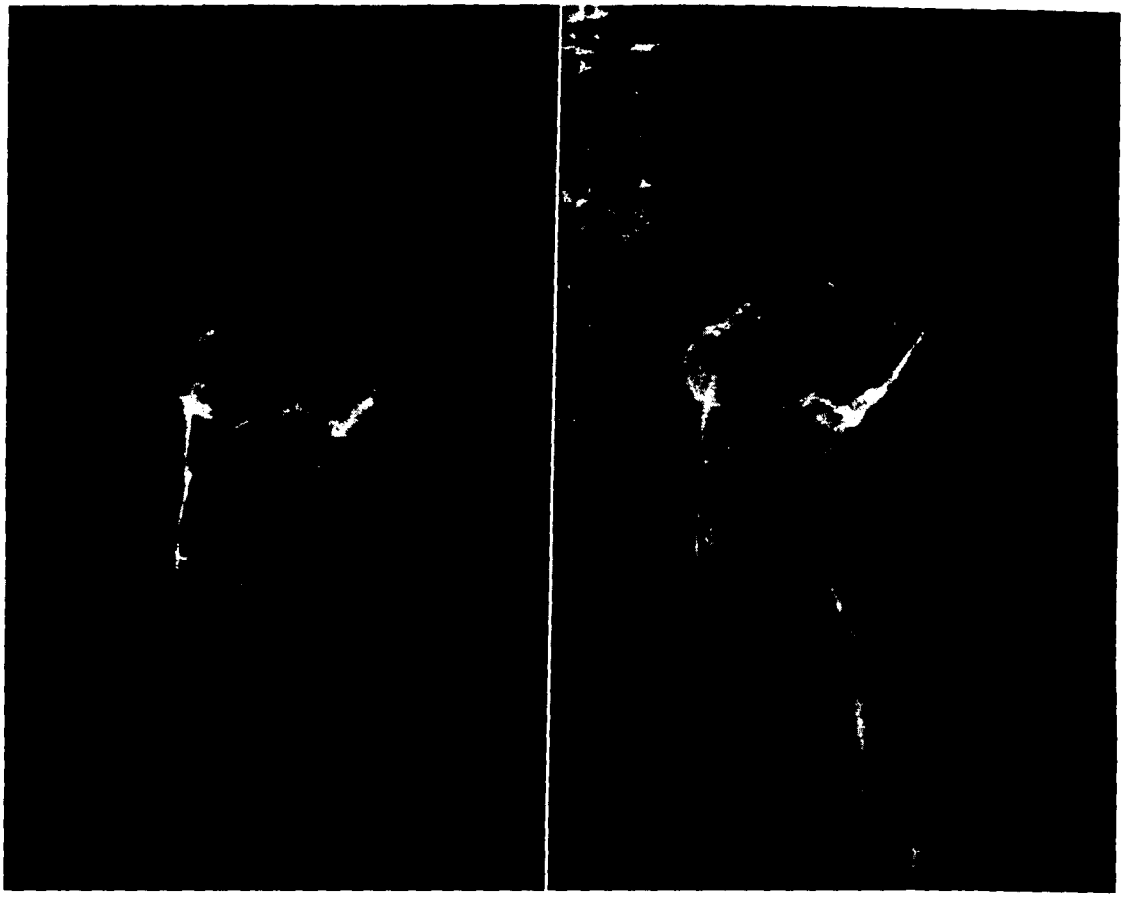

Fig. 1. Case v. J.C. The pelvis shows extensive involvement by multiple myeloma with biopsy defect and pathologic fracture involving the left ilium. The bone lesions showed no progress in the eight months following treatment.

histopathologic changes consistent with this treatment. Normal tissues that had been subjected to total body irradiation showed no gross or microscopic effects of such irradiation.

Laboratory data during the treatment period showed maximal depression from the 200 r dose.

	Initial	*Low*	*Final (7 wk.)*
Hb.	12.5 gm.	8.7 gm. @ 3 wk.	8.9 gm.
R.B.C.	4,000,000	2,700,000 @ 3 wk.	2,800,000
W.B.C.	11,000	2,600 @ 3 wk.	5,200
Platelets	150,000	50,000 @ 5 wk.	92,000

The differential white blood cell count at three weeks showed an increase in lymphocytes but the absolute lymphocyte count remained approximately constant.

Case v. J.C. (AX-5284) A white male, aged thirty-five, had suffered a fracture of cervical spine in an accident three years previously and extensive lesions of multiple myeloma were discovered at that time. A year later the diagnosis was confirmed by biopsy. Except for a gradual weight loss of 45 pounds, the patient remained well, subjectively, until four months before admission. From this time he was confined to bed by severe back pain and increasing weakness. Roentgenograms showed compression fractures of several vertebral bodies and he was transferred to the hospital on a Stricker frame. On July 22, 1953, he received 200 r (skin dose)

total body irradiation (250 kv., half-value layer 2.3 mm. Cu, target skin distance 400 cm.). Immediately after treatment he vomited once without nausea. He ate his noon day meal two hours later and had no further reaction. Pain relief was evident the day following treatment, and by the third day appetite was improved. On Aug. 13, 1953, a second dose of 200 r, under the same conditions as the first, was administered. This time there was no nausea or vomiting and there were no new complaints. One week later he was completely relieved of back pain and was up and about the ward voluntarily. His only complaint was of pain in feet and ankles. There were no roentgen changes evident in the bones of this area and the pain apparently was due to ambulation after five months in bed. He received five transfusions of 500 cc. each during September and was then discharged home. He has received no further treatment and now talks hopefully of returning to work (Fig. 1).

Laboratory data during this period were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	8.3 gm.	6.0 gm. @ 5 wk.	11.0 gm.
R.B.C.	3,800,000	1,700,000 @ 5 wk.	3,200,000
W.B.C.	6,000	550 @ 5 wk.	8,250
Platelets	295,000	13,000 @ 6 wk.	210,000
Iron turnover half time	0.5 hr.	1.0 hr. @ 3 wk.	0.8 hr.

The differential white cell count at five weeks showed a doubling in the percentage of lymphocytes.

For both radiation therapy and chemotherapy, the ultimate effects are mediated by intracellular chemical changes. For this reason the two may be compared on terms of tolerance of the individual response of the disease, and factors governing their role in application.

Tolerance to radiation does not lend itself to ready measurement. In Court Brown's[3] series of 60 patients, he was able to define three phases of radiation sickness: (1) the latent period extending from the time of treatment to the onset of symptoms; (2) a period of acute disturbance lasting from one and one-half to four hours after the onset of symptoms; (3) recovery period extending as long as four or five days. The length of the latent period was inversely proportional to the period of acute symptoms and was used as an index of severity of reaction. In the patients presented here, a pattern of symptoms was not apparent; nausea and vomiting were inconstant and their condition before treatment was such as to mask any minor degree of weakness or lethargy. From a symptomatic point of view, the reaction to single doses up to 200 r was less than would be anticipated with conventional doses of nitrogen mustard, and the hematopoietic depression was acceptable as compared with this agent.

The response of the patients' disease can only be considered as indicative that total body irradiation in single doses up to 200 r has therapeutic possibilities. The tolerated dose is beyond that necessary or desirable for leukemia but is in the effective range for lymphosarcoma and multiple myeloma. The patient who received 200 r on two occasions in three weeks had a clinical response that could be described as impressive.

No agent currently in use for treatment of generalized cancer is offered with intent to cure. Even increased survival as a result of therapy is difficult to confirm. Under these circumstances the principal benefit of treatment is early relief of signs and symptoms and this benefit may be mitigated by the severity of side effects of treatment, prolongation of treatment or delayed response to treatment. In all these respects, the administration of single doses of total body irradiation has some advantage.

There is an additional advantage in the matter of dose. Prescription of radiation dose is unique in its precision. It is possible under controlled conditions to deliver a desired amount to any tissue or to calcu-

late what has been delivered to any site. To relate dose and effect, it is desirable to determine dose at the site where effect is produced, so that a given result can be repeated or modified. Prescription of dose of pharmaceutical agents is usually on the basis of body weight, administered intravenously, orally, or intramuscularly. In the processes of absorption, dilution and transportation, the amount of the agent finally producing an intracellular chemical effect must be subject to wide and unpredictable variations. If the clinically effective dose closely approaches the tolerance dose, it is desirable to have knowledge and control of the amount of concentration of an agent at the cellular level where its effect is exerted.

SUMMARY

Total body irradiation in a single exposure up to 200 roentgens of 250 kilovolt roentgen rays may be safely administered to patients with generalized cancer. Considered as one form of systemic therapy rather than as an alternative or competitive method of treatment, total body irradiation in doses of this order is a useful addition to the management of advanced cancer.

Vincent P. Collins, M.D.
1200 M.D. Anderson Blvd.
Houston, Texas

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