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SYSTEMIC AND CLINICAL EFFECTS INDUCED IN 263 CANCER PATIENTS BY WHOLE-BODY X-IRRADIATION WITH NOMINAL AIR DOSES OF 15 TO 200 R

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INTRODUCTION

Some effects of human whole-body irradiation are known from the following sources: first, studies of atomic bomb casualties (1); second, findings obtained from persons involved in nuclear accidents (2); and third, observations made on patients receiving therapeutic radiation (3, 4, 5). Singly these data are of limited value because either the dose is ill-defined or the subject is not a healthy human being; collectively, however, they allow reasonable conclusions that will become increasingly accurate as more observations are reported. The present study, originating from therapeutic considerations alone, attempts to contribute such additional information.

It has been established that chemotherapy, for a transitory period only, may relieve pain and cause subjective improvement in cases of incurable generalized tumors, quite frequently even those of low radiosensitivity. Because of its less severe side effects, whole-body x-irradiation has been suggested as a superior method for the palliative treatment of such patients (6). Is whole-body x-irradiation, here, an effective procedure? If so, how high is the dose that can or must be administered to obtain beneficial results?

To answer these questions, a long-term study was initiated in 1951 and continued until 1956. From the beginning it was realized that significant clinical benefit could be expected, if at all, only at a dose level bordering the clinical threshold dose or clinical tolerance dose, beyond which serious complications might occur. Paucity of knowledge about this important range necessitated cautious exploration beginning at rather low doses. In the range from 15 to 25 r, whole-body roentgen therapy commonly has been used in the management of leukemias (7); on the basis of this experience, similar small doses were applied first to other, less radiosensitive, generalized tumors. With additional experience gained from careful observation of the patients, the dose was raised in later cases in steps of 25 r. The exploratory phases of the inquiry comprised 233 patients exposed to doses ranging from 15 to 200 r; the final phase consisted of a series of 30 patients who received 200 r. The nature of this study necessitated extensive general, clinical, and laboratory surveillance of the irradiated persons to detect promptly any harmful effect induced by the treatment.

The present report describes in some detail the findings obtained in the final phase of the investigation, but only the most essential observations made during the exploratory phases. Furthermore, it emphasizes those aspects of the problem which are of general radiobiologic interest; a strictly clinicotherapeutic evaluation will be given elsewhere (8).

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METHOD

Chronologic evolution of study and standard for case selection

During the first two years, relatively low doses (15 to 75 r) of whole-body x-irradiation were employed largely as adjuvants to limited field exposure or hormone treatment, and were administered either concomitantly with or shortly before initiation of the conventional therapeutic procedure. For this first exploratory phase, therefore, patients were selected whose disease was in such a state that cure or at least definite palliation could still be expected from established methods of treatment. These low doses were tolerated well enough to raise hope that higher doses of whole-body exposure, similar to nitrogen mustard, might prove useful as an independent form of palliative therapy.

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1 9.5

Thus, in a second phase, cautious exploration of the dose range from 100 to 200 r was started. Understandably, the greater possible risk necessitated now the selection of patients whose disease had advanced to such a state that, in general, significant benefit could not be expected from conventional procedures other than systemic ones. Therefore, in combination with whole-body exposure, additional forms of treatment were administered less frequently. Again the tolerance was such that exposure to 200 r seemed justified for a last group of 30 patients. In this final phase of the study standards for selection of cases were even more severe. All patients showed such an advanced state of disease (figs. 1 and 2) that cure by conventional means was regarded as completely hopeless. Of the 30 cases—prior to whole-body irradiation—21 had received

FIGURE 1

Unclassified malignancy. Numerous subcutaneous tumor masses are widely disseminated over the anterior chest wall. The photo depicts condition prior to whole-body exposure to 200 r (case 5).

neither radiotherapy nor chemotherapy, 8 had been subjected to either one or both of the treatments, and 1 had already received whole-body irradiation. Composition of the 200-r group varied widely with respect to age and type of malignancy (table I). At the time of irradiation these patients were still able to walk and perform light physical tasks; they knew about the advanced state of their disease and the experimental nature and possible risks of the proposed radiotherapy.

General procedure

After conclusion of the first exploratory phase (15 to 75 r), a routine procedure was adopted as follows: the patients were observed for an initial 2-week period that was divided into three sections. A preradiation interval of 4 days was followed by whole-body exposure on the fifth day and by a postradiation interval of 9 days. During these 14 days, hospitalization occurred only in those cases where it was required by clinical considerations or lack of housing facilities; in the majority of cases the patients continued to live on the outside and appeared daily at the clinic for check-up or treatment. Hematologic data from the peripheral blood were obtained daily with ordinary laboratory methods. No attempt was made to standardize diet or physical activity of the patients. Following completion of the initial 2-week period, the pattern of observation varied widely. The few patients who remained hospitalized could be seen and examined daily. Of those released, the majority appeared more or less regularly for follow-up examinations, frequency of visits depending largely on distance between hospital and home town; approximately 15 percent were lost from sight.

Irradiation

A Maxitron (G.E.) operated at 250 kvp with a Thoraeus III filter, providing a 3.0 mm. copper HVL, served as x-ray source. The tube was used without a diaphragm, and the beam was aimed horizontally at a wall 240 cm. away. Sitting laterally to the beam the patient, in a slumped-over position, covered approximately one-half of the circular area outlined by the cross section of the beam (fig. 3). The distance between x-ray source and midline of the patient was 205 cm. At this distance the dose rate in air averaged 3.8 r/minute. After one-half of the exposure had been delivered—100 r based on

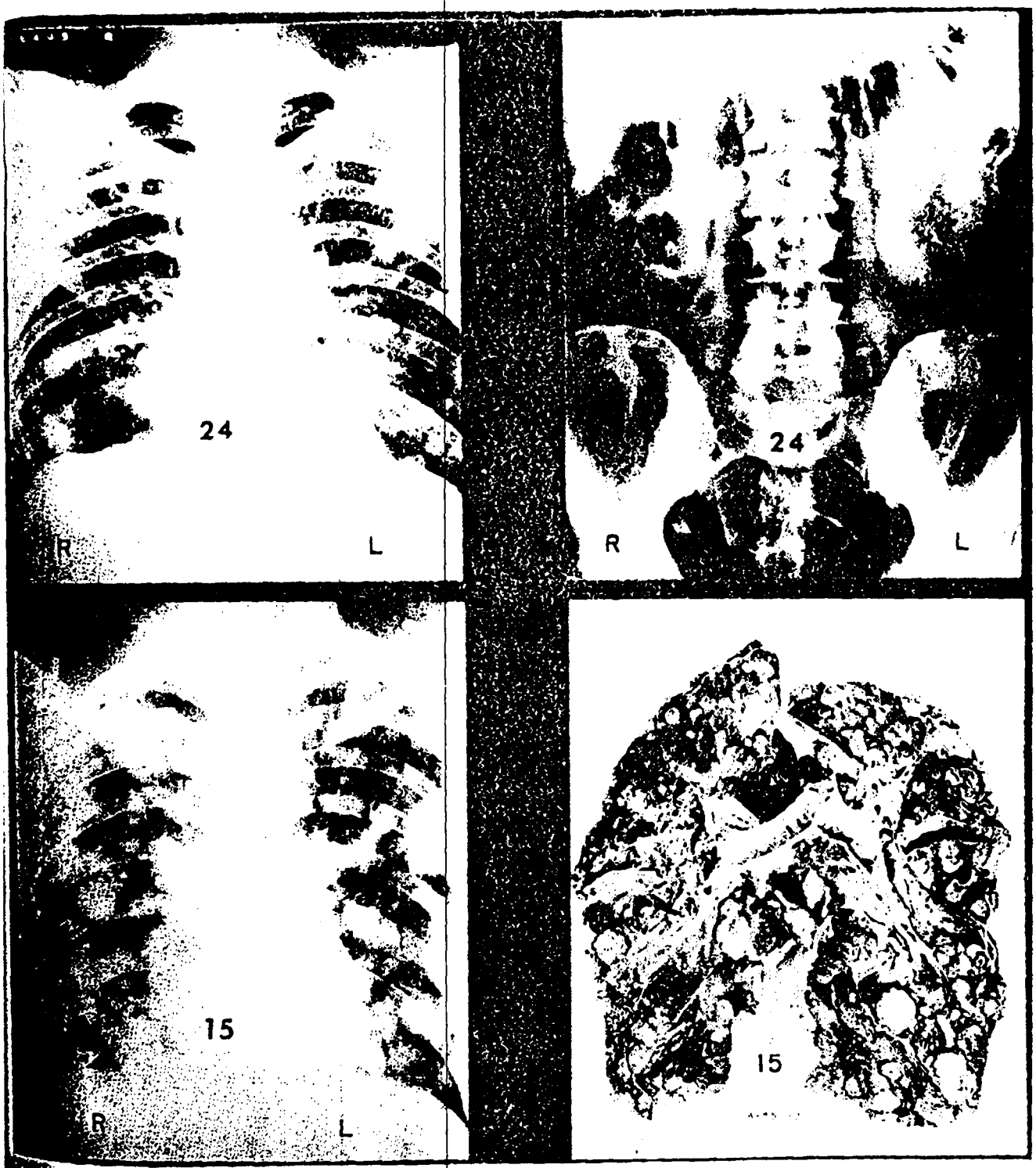

FIGURE 2

Composite picture.
Upper left: Roentgenogram of chest taken prior to whole-body exposure. Several tumor masses are evident in the left and right lung fields (case 24).
Upper right: Roentgenogram of abdomen and intravenous pyelogram taken prior to whole-body exposure. The left kidney has been replaced by a large tumor mass (case 24).
Lower left: Roentgenogram of chest taken prior to whole-body irradiation. Tumor infiltrations throughout left and right lung fields are visible (case 15).
Lower right: Photo of lungs after autopsy. The cancer masses have replaced most of the normal lung tissue (case 15).

air dose at midline—the patient was turned around 180 degrees and exposed to the other half dose. Total exposure, performed in a single session, required approximately 51 minutes. Detailed analysis of dosimetric problems encountered in this study, determination of dose distribution throughout the body, and estimation of integral doses have been reported separately (9).

RESULTS

On the ensuing pages the findings are arranged in sections. In the first section observations made on the final 200-r group are reported in some detail since in this group effects produced by irradiation could be separated to a large extent from those attributable to the disease, and since these patients were

TABLE I

Survey in chronologic order of the final group of 30 patients who received single whole-body exposure to a nominal air dose of 200 r.

Case No.	Age (years)	Histologic diagnosis	Origin of tumor	Survival (months)
6	50	Adenocarcinoma	Undetermined	11.6
7	76	Adenocarcinoma	Kidney	1.0
8	78	Melanoma	Skin	1.7
9	64	Undifferentiated carcinoma	Bronchus	0.5
10	46	Melanoma	Eye	13.5
11	33	Ewing's sarcoma	Rib	7.4
12	64	Squamous carcinoma	Bronchus	1.1
13	65	Squamous carcinoma	Bronchus	1.0
14	63	Squamous carcinoma	Bronchus	8.6
15	23	Plurigeneric carcinoma	Testis	0.4
16	57	Squamous carcinoma	Tonsil	14.2
17	59	Undifferentiated carcinoma	Bronchus	1.0
18	25	Plurigeneric carcinoma	Testis	6.8
19	52	Squamous carcinoma	Bronchus	11.0
20	50	Squamous carcinoma	Bronchus	5.2
21	57	Undifferentiated carcinoma	Bronchus	0.5
22	51*	Lymphosarcoma	Undetermined	19.2
23	48	Undifferentiated carcinoma	Bronchus	3.3
24	56	None	Kidney	0.9
25	61	Undifferentiated carcinoma	Bronchus	3.4
26	43	Adenocarcinoma	Bronchus	2.6
27	75	Squamous carcinoma	Skin	1.5
28	26	Plurigeneric carcinoma	Testis	0.5
29	52	Adenocarcinoma	Colon	4.1
30	41	Adenocarcinoma	Adrenal	8.2
31	60	Adenocarcinoma	Liver	3.6
32	62	Undifferentiated carcinoma	Bronchus	3.5
33	67	Adenocarcinoma	Pancreas	1.3
34	55*	Hodgkin's disease	Undetermined	3.3
35	61*	Adenocarcinoma	Breast	0.8

*Female.

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watched more closely than the others. In the second section, findings obtained from the exploratory groups are described rather cursorily; a more exhaustive treatment seems uncalled for since symptoms induced by the advancing disease frequently obscured the milder ones possibly produced by radiotherapy. In the third section, observations are presented for a few patients who received two separate doses of whole-body irradiation.

1. Final 200-r group

Early reactions to irradiation with 200 r were relatively mild in most instances. Only 2 of the 30 patients composing the final group became nonambulatory within the first postradiation week; one of these (case 18) had to be confined to bed soon after treatment and had to remain there throughout the next day because of nausea, vomiting, and weakness; the other (case 21) became bedridden owing to accentuation of a cardiac decompensation which existed before the radiotherapy. The remaining 28 patients experienced during the first 3 days posttreatment a more or less pronounced impairment as described in the next paragraph.

Nausea and vomiting. Upon interrogation, all but 3 of the 30 patients reported an impairment of condition which was described as either fatigue, decreased energy, drowsiness, or malaise, and which was accompanied by a loss of appetite. Usually, this condition developed within a few hours posttreatment and progressed to nausea or actual vomiting in most cases. Invariably, the latter symptoms then overshadowed the previous ones to such a degree that a clear separation was impossible.

Among the 30 final 200 r cases irradiation was not followed by vomiting in 13, and in at least 5 of these, not even by nausea (table II). Only one of the 13 patients was receiving antinausea medication since he continued to take four times each day the 25 mg. doses of chlorpromazine hydrochloride prescribed earlier by his referring physician; this fact was discovered at a later interrogation. In the majority of the remaining 17 cases nausea and actual vomiting appeared within the first few hours following exposure (table III) and subsided after the 3d postradiation day. Among these patients, 10 showed complaints of such a moderate degree that antiemetic treatment

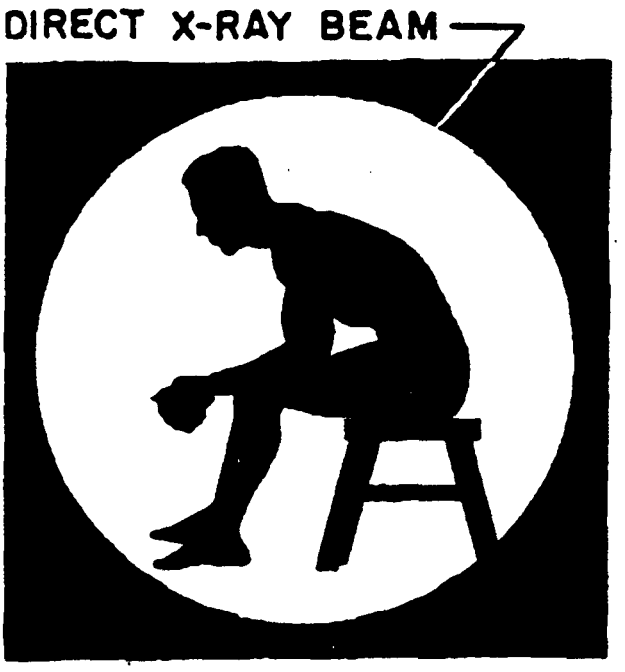

FIGURE 3

Schematic drawing of patient during exposure which shows that the entire body is well within the central homogeneous area of the direct beam and that no body part enters the fringe zone where x-ray intensity diminishes.

TABLE II

Incidence of vomiting and nausea induced in 30 patients within 72 hours following whole-body irradiation with 200 r.

Did vomit	
Antiemetic and venoclysis required	2
Antiemetic alone required*	5
Antiemetic not required	10
	17
Did not vomit	
Nausea absent	6
Nausea present	5
Not recorded	2
	13

*In all but one of these cases antiemetic therapy was required during the preradiation period also.

was not indicated; 5 required chlorpromazine hydrochloride, usually in oral doses of 25 mg. every 6 hours; and 3 exhibited reactions sufficiently severe to necessitate both antiemetic medication and parenteral fluid replacement. In all cases these measures yielded prompt improvement. It must be emphasized that it was impossible to analyze to what extent nausea and vomiting, not infrequently occurring spontaneously in such a group of patients, were caused by irradiation alone, or by the combination of radiotherapy and disease.

As revealed by numerous animal experiments the body weight must be considered a rather sensitive indicator of radiation-induced impairment of nutrition. Therefore, daily weight measurements were performed until the 9th day postradiation on 11 of the 200-r patients. During this time no appreciable change in mean body weight of the group occurred; statistical evaluation of the data showed no significant trend. Among the group only one patient, case 18, developed appreciable weight loss (7 pounds) within the first 24 hours after radiotherapy; this obviously was caused by profuse vomiting and normal weight was restored by the 4th postradiation day.

Thus it must be concluded that anorexia, nausea, and vomiting only occasionally reached such a degree as to compromise satisfactory nutrition of the patients.

Body temperature and blood pressure, recorded systematically in some of the cases only, revealed no significant change. However, the value of these observations must be considered as rather limited since the activity of the patients was not controlled.

To illustrate the points discussed so far, excerpts are taken from the histories of 2

TABLE III

Distribution of vomiting during first 72 hours following whole-body irradiation with 200 r.

Case No.	First emesis (hours post-irradiation)	Frequency of emesis		
		First 24 hours	Second 24 hours	Third 24 hours
6	1	4	4	3**
7*	Not recorded	2**	0	0
9	58	0	0	3
13	3½	9	12	4**
15	1	1	0	0
16	28	0	4	0
17*	Not recorded	1**	1**	1**
18	2	5	2**	0**
19	60	0	0	1
21	2¼	2	0	0
22	2	1	0	0
24	30	0	1	0
28*	Immediate	4**	0**	0**
31	4	1	0	0
32	1	3	0	0
34*	Not recorded	7**	4**	0**
35	60	0	0	1

*Administration of chlorpromazine hydrochloride during preradiation period.
**Treated with chlorpromazine hydrochloride.

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patients, showing the mildest and the severest initial reactions, respectively. *Case 11*, a 33-year-old minister, had Ewing's sarcoma originating from the posterior segment of the right 4th rib. Resection and two subsequent courses of local roentgen therapy had failed to prevent recurrence. On 14 December 1954 he received 200 r whole-body x-irradiation; the exposure was started at 6 o'clock in the morning. After completion of the treatment, examination, and laboratory studies, the patient left the hospital at noon. He had a meal and subsequently a one-hour rest as was his custom, then worked at ministerial duties until 9 o'clock in the evening. On each of the succeeding days he devoted at least 10 hours to his professional obligations. Upon interrogation, he admitted having had a few episodes of "minimal nausea" during the first 2 days after treatment, but anorexia, vomiting, or other complaints were denied. *Case 18*, a 25-year-old male, had mixed testicular embryonal carcinoma and seminoma with bilateral pulmonary metastases. Since two trials of local roentgen therapy had produced only temporary improvement, he received 200 r whole-body x-irradiation on 18 April 1955. The treatment was completed at 7:30 a.m. Approximately 2 hours later severe nausea, vomiting, and prostration developed. During the first 24 hours following exposure he vomited 5 times and lost 7 pounds in body weight. Most of the vomiting occurred within the first 8 hours, and he was able to eat and retain supper that night and breakfast next morning. Extreme weakness—necessitating stretcher transport—and moderate nausea persisted however throughout the first postirradiation day. On the following day, therefore, he received intravenously 1 liter of normal saline solution with 10 percent dextrose, and was started on 25 mg. doses of chlorpromazine hydrochloride, four times each day. Thereafter recovery was rapid. On the second postradiation day he vomited only twice and regained 4 pounds of his lost weight. No further parenteral fluid supply was required. Ambulation was resumed on the third postradiation day. On the fourth day, his body weight had returned to normal level, and chlorpromazine medication was discontinued.

Effect on the disease. After the third postirradiation day the initial reactions—essentially fatigue, anorexia, nausea, and vomiting—had subsided, and the general condition of most of the patients had returned to the preradiation level. Shortly thereafter approximately 30 percent of the group claimed subjective improvement at least temporarily; frequently, however, these claims could not be supported by objective findings. In most cases psychologic rather than clinical factors might have been responsible for the alleged transitory improvement, and in only three instances could a somewhat more concrete effect be established. *Case 11* stated that within 4 days after exposure his pain vanished for the first time in 4 months; for 10 days he did not use analgesics and narcotics necessary prior to radiotherapy; following this transitory improvement, however, he relapsed to his preradiation condition. *Case 33*, previously experiencing severe right shoulder and arm pain believed due to large metastatic masses in the right supraclavicular fossa and right axilla, claimed marked, although incomplete, relief developing on the third postradiation day. This relief coincided with a questionable slight decrease in size of the tumor masses; pain returned 2 weeks later when the tumor began to advance again. *Case 22*, a negress, suffered from generalized lymphosarcoma. Following irradiation she reported a gain in general strength, substantiated by an increase in body weight and by a slow but definite shrinkage of the tumor masses in rectal mucosa and nasopharynx. About 2 months later she was able to resume work as housewife, farm helper, and practical nurse. Further treatment was not required. This improved state persisted until approximately 2 weeks prior to her death that occurred one year and 7 months postirradiation.

In summary, 200 r whole-body x-irradiation produced a definite transitory amelioration of the disease in 3 cases, and a questionable improvement in several additional patients.

Hematology. The hematologic data obtained during the 2-week initial observation period showed definite radiation-induced changes (table IV). For statistical evaluation the group means of the measurements on each postradiation day were compared with the corresponding values determined 2 days prior to exposure, and Student's t-test was applied to the differences. This procedure yielded the following result: significance on the 0.01

level was reached for the total white cell count, on the 7th postradiation day; for the lymphocyte count, on the 2d postradiation day; and for the platelet count, not at all. Hence it may be concluded that, with a probability greater than 99 percent, the drops in leukocyte and lymphocyte counts were not the result of chance alone. Red cell count, hemoglobin, and reticulocyte count (not tabulated) did not show significant changes. Results of iron-59 clearance and uptake studies were treated in a separate report (10).

In 4 cases long-term observations could be performed regularly enough to allow graphic representation (figs. 4-9). The total white count (fig. 4) reached a minimum between the 4th and 6th postradiation weeks—the sudden rises in cases 33 and 27 must be regarded as terminal phenomena; the lymphocyte count (fig. 5), exhibiting the earliest and most pronounced drop, showed little indication of recovery; and the platelets (fig. 6) essentially paralleled the white count except for absence of the terminal rises. Red cell count (fig. 7), hemoglobin (fig. 8), and hematocrit (not represented) displayed a tendency toward a gradual decline, while the reticulocytes (fig. 9) showed an irregular behavior.

Sixteen additional patients could be followed, although more sporadically, for a sufficient length of time to permit analysis. These cases, together with the 4 described in the previous paragraph, were treated statistically. The result was as follows: in 8 cases leukopenia with less than 2,500 white cells/mm.^{3} developed; the mean time interval between exposure and lowest white count was 32 days, with a range from 11 to 52 days. Recovery above the 2,500 cell level occurred after a mean postradiation time interval of 46 days, with a range from 12 to 81 days. Thrombocytopenia—platelet count below 70,000/mm.^{3}—was encountered in

TABLE IV

Effect of 200 r whole-body x-irradiation on the number of white blood cells, lymphocytes, and platelets in 1 mm.^{3} of blood. Means and standard deviations obtained from a group of 30 patients have been tabulated.

Time (days)	WBC (thousands/mm.^{3})		Lymphocytes (thousands/mm.^{3})		Platelets (thousands/mm.^{3})	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Pre-radiation						
1	9.62	4.48	1.45	.77	150	66
2	9.32	3.52	1.43	.82	154	68
3	9.33	4.27	1.36	.67	151	64
Irradiation						
0	9.65	3.85	1.16	.53	168	64
Postradiation						
1	9.14	3.45	1.00	.47	—	—
2	7.99	2.50	.88	.36	154	58
3	8.43	3.63	.81	.33	—	—
4	8.09	2.88	.73	.35	142	64
5	8.06	3.28	.78	.35	—	—
6	7.39	2.77	.64	.28	137	54
7	7.05	2.39	.69	.27	116	56
8	6.76	2.29	.71	.34	139	70
9	6.50	2.29	.69	.33	—	—
10	6.49	2.17	.68	.33	—	—

WHITE CELLS IN THOUSANDS/mm^3 OF BLOOD

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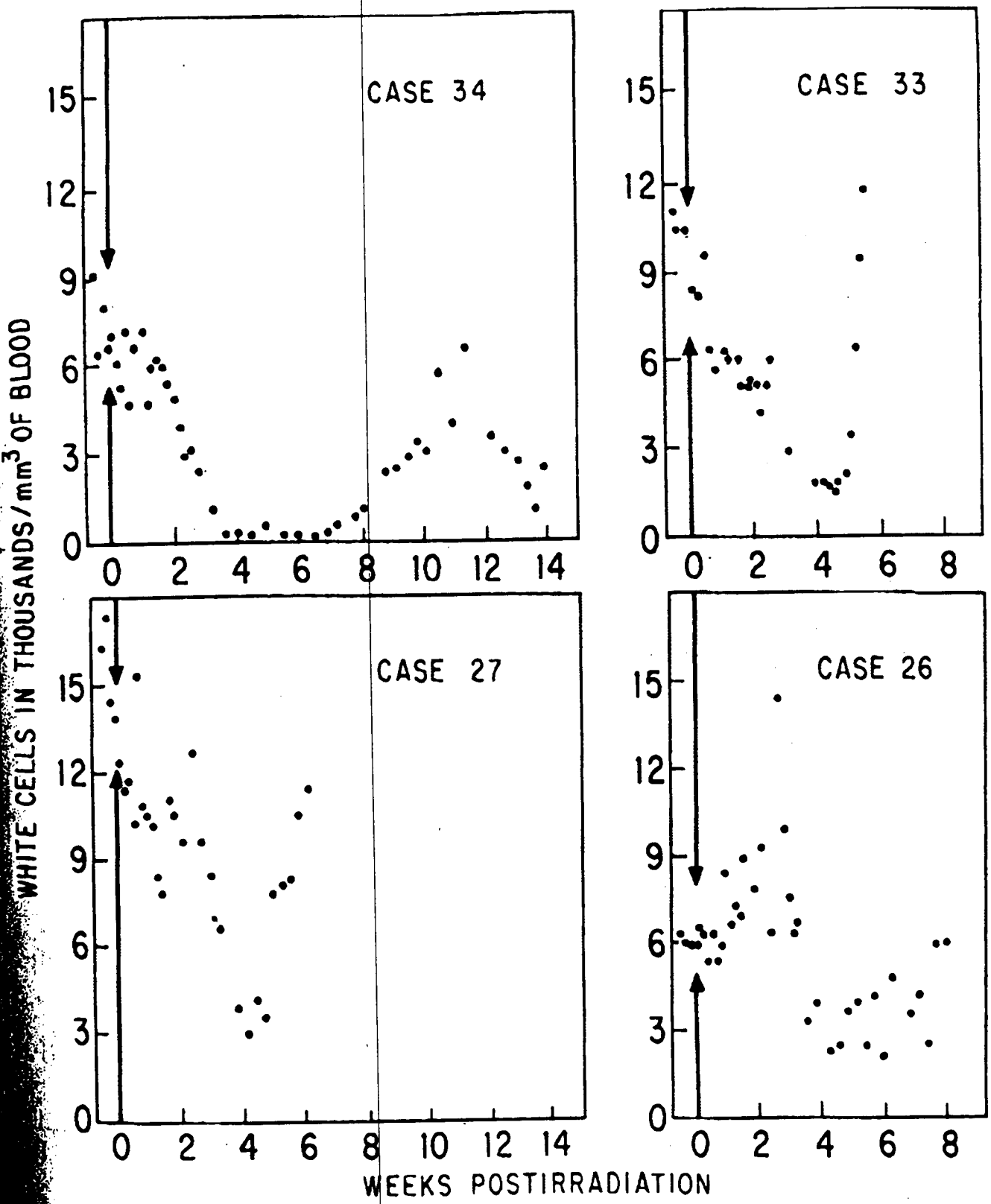

FIGURE 4

Effect of 200 r whole-body x-irradiation on the total white blood cell counts of 4 patients. Each dot represents one single determination. The arrows indicate the day of exposure.

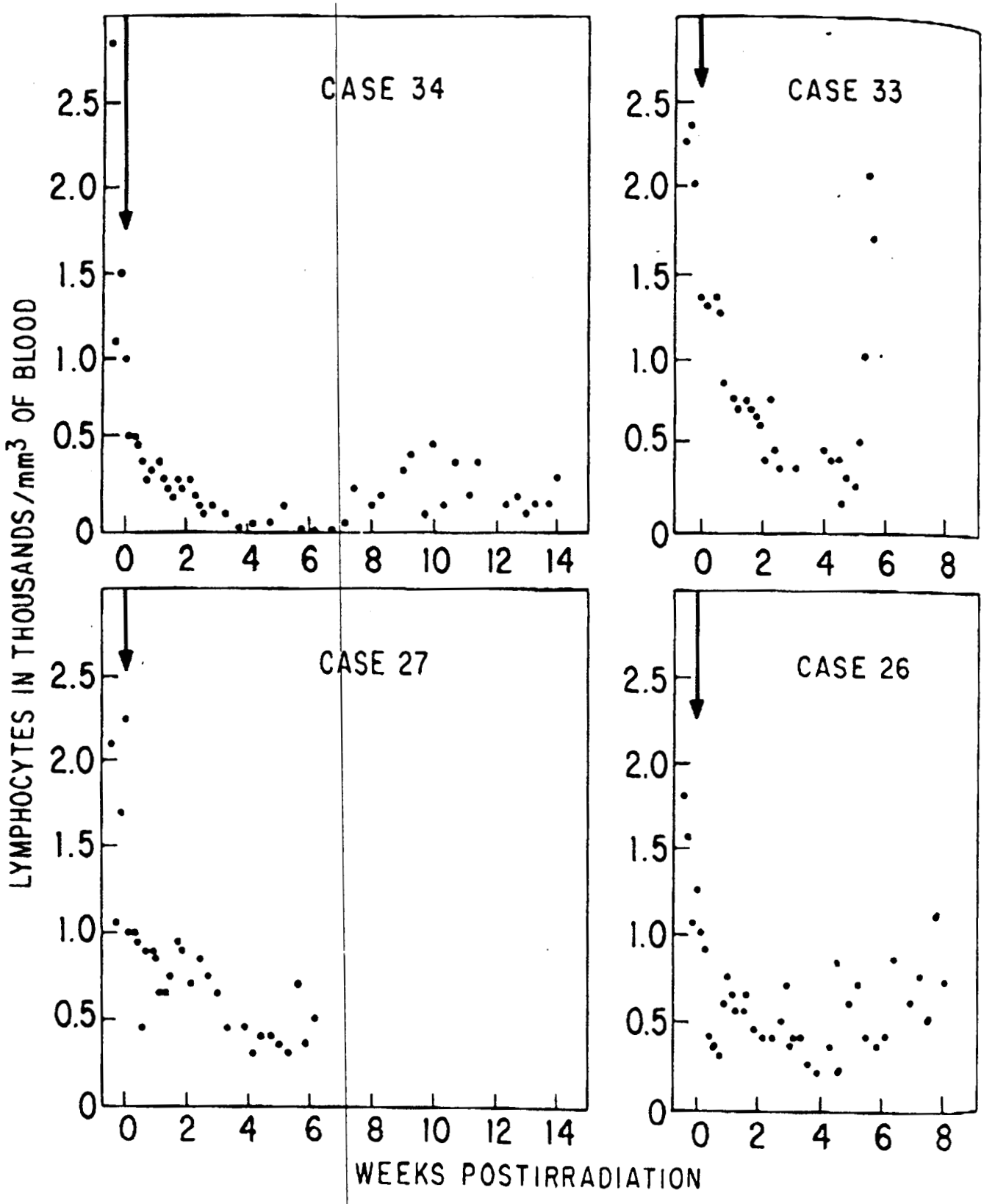

FIGURE 5

Effect of 200 r whole-body x-irradiation on the lymphocyte counts of 4 patients. Each dot represents one single determination. The arrows indicate the day of exposure.

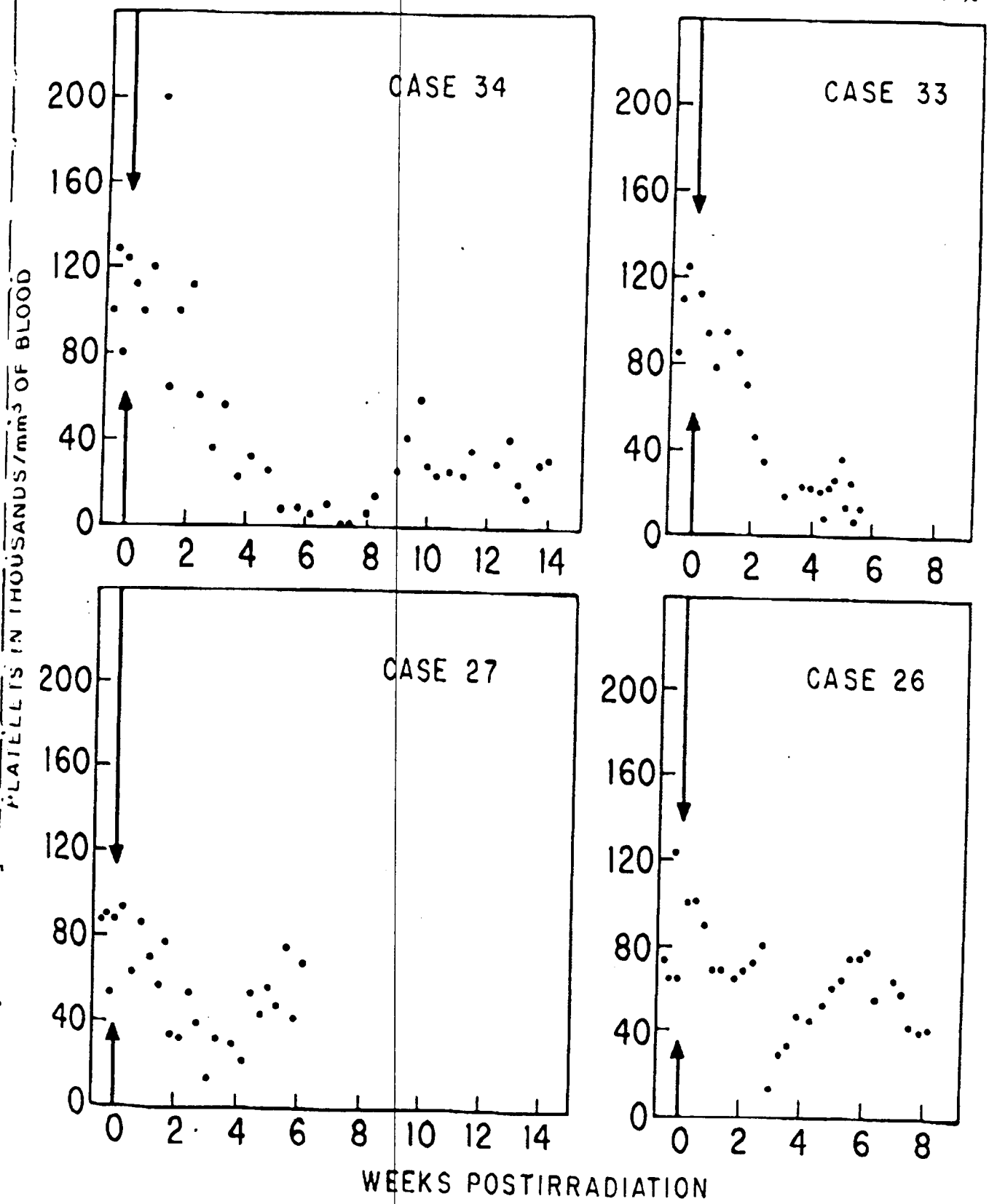

FIGURE 6

Effect of 200 r whole-body x-irradiation on the platelet counts of 4 patients. Each dot represents one single determination. The arrows indicate the day of exposure.

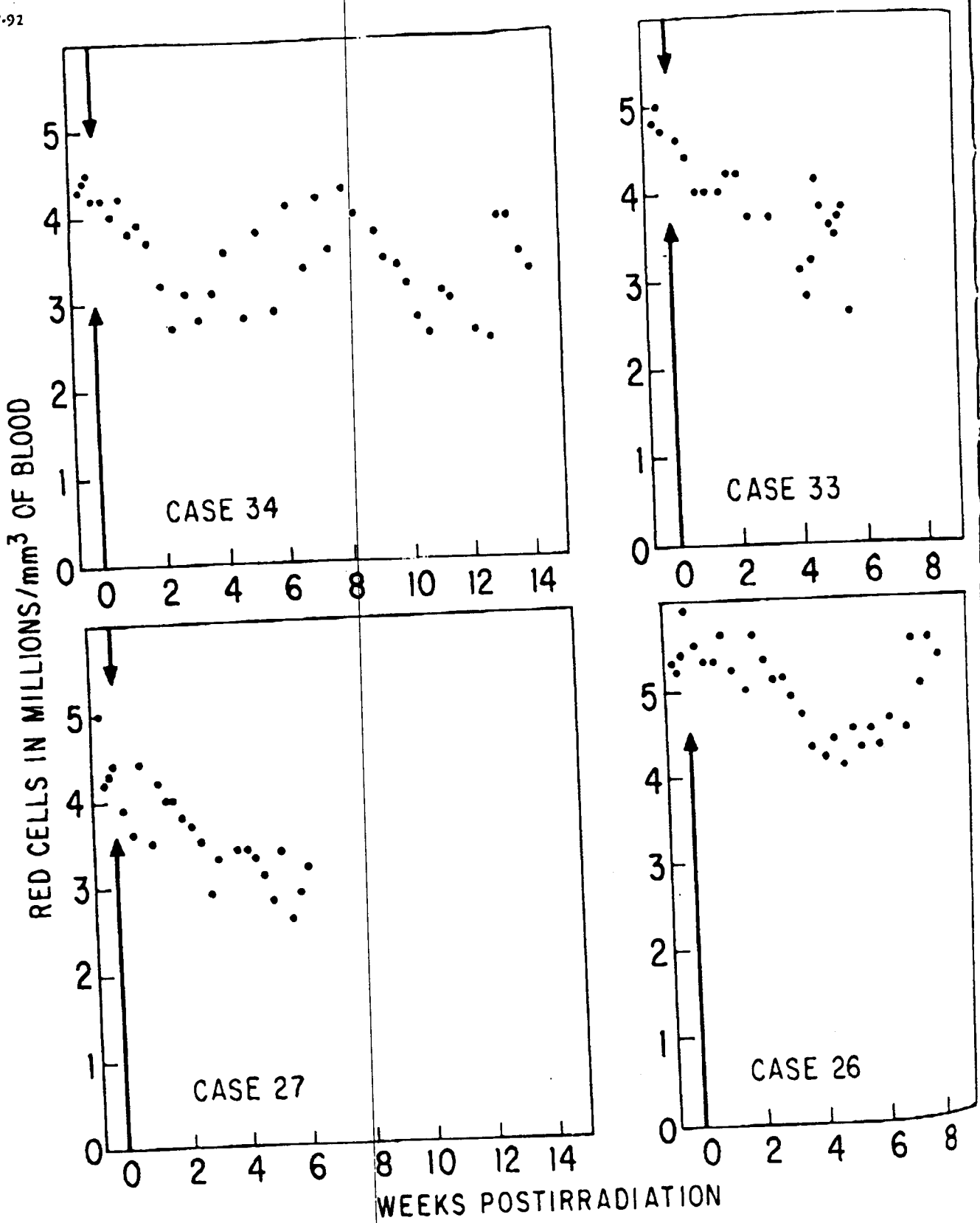

FIGURE 7

Effect of 200 r whole-body x-irradiation on the red blood cell counts of 4 patients. Each dot represents one single determination. The arrows indicate the day of exposure.

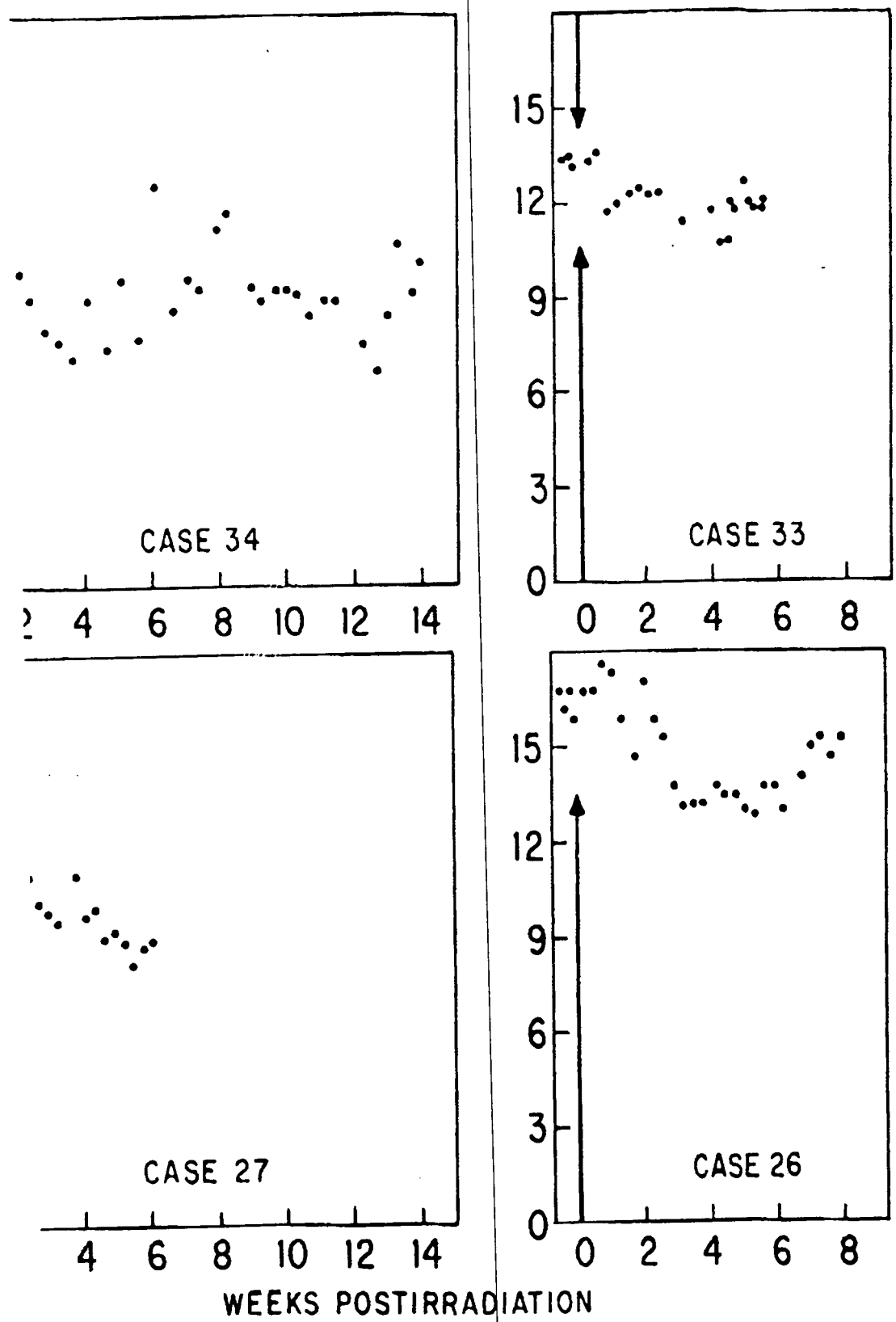

FIGURE 8

vhole-body x-irradiation on the hemoglobin levels of 4 patients. Each dot represents one on. The arrows indicate the day of exposure.

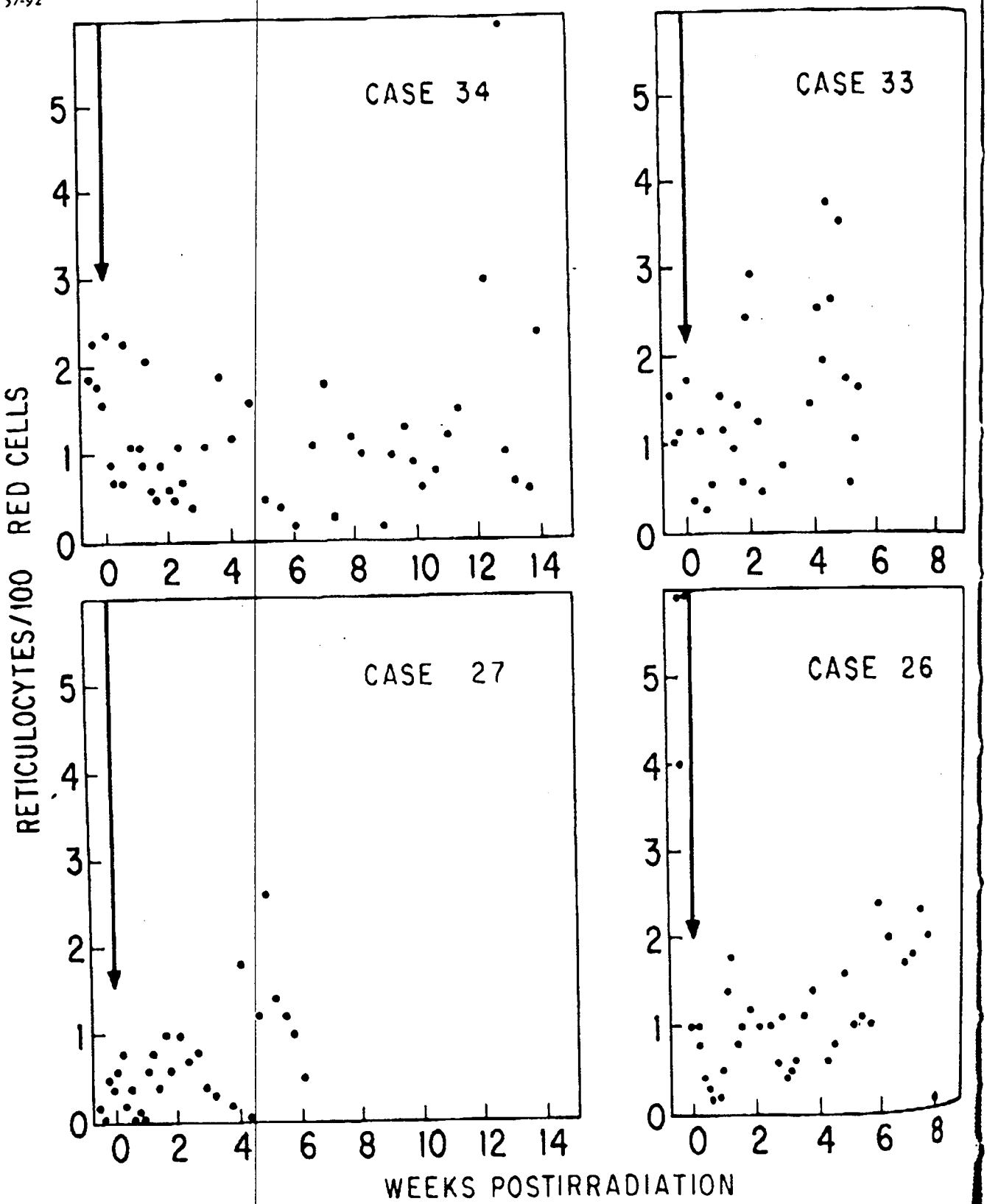

FIGURE 9

Effect of 200 r whole-body x-irradiation on the reticulocyte counts of 4 patients. Each dot represents a single determination. The arrows indicate the day of exposure.

all 20 patients; however, it existed prior to irradiation in 4 cases. The mean time span elapsing between exposure and lowest thrombocyte count was 25 days, with a range from 8 to 50 days. Definite recovery above the 70,000 level occurred only in 5 cases after a mean interval of 59 days, with a range from 28 to 97 days. Anemia—a hematocrit reduction of more than 5 volume percent as compared to the preradiation values—developed in 12 of the 20 patients. A definite recovery occurring from the 11th postradiation week onward could be demonstrated in only 2 of these cases. Since anemia is a common occurrence in terminal cancer patients, it was difficult to judge the causative or attributive role of irradiation in producing this long-lasting depression of red cells.

Complications. Macroscopic bleeding occurred subsequent to irradiation in 19 of the 30 cases; however, it should by no means be inferred that all, or even many, of these hemorrhages were due to radiotherapy. Hemoptysis was by far the most common type of bleeding. It occurred in 15 patients whose lungs, with 3 exceptions, contained either primary or metastatic tumors. In 7 of the 15 patients, including the 3 without known lung involvement, there was no history of hemoptysis prior to treatment, and the postradiation hemoptyses were unimportant with respect to blood loss. In the remaining 8 patients, all with known lung involvement, hemoptyses preceded as well as followed treatment; after irradiation the bleeding was somewhat increased in 1, and seriously accentuated in 3 of these cases.

Postradiation bleeding from extrapulmonary tumor sites occurred in 3 cases; however, it had already been present prior to irradiation. Postradiation epistaxes without apparent cause were reported by 4 patients. In 3 instances the bleeding was brief and self-limited; it did not require treatment and did not recur. The remaining case was enigmatic. The patient had had a cerebrovascular accident and occasional mild nosebleeds prior to irradiation. Epistaxes remained occasional until the 74th day after irradiation when they began to occur daily. Thereafter they persisted despite treatment by his family physician. The individual roles of disease and irradiation in bringing about the patient's epistaxes could not be established.

Bleeding into the skin—petechiae and/or ecchymoses—were seen in 4 patients; in each of these cases, however, whole-body x-irradiation was considered only one of the causative factors for the general hemorrhagic disorder. The bleeding occurred in a first case with terminal cardiac decompensation, in a second case with additional administration of three large doses of nitrogen mustard, in a third case with tense edema of the legs (ecchymoses in skin of legs only), and in a fourth case with additional rather high doses of limited field irradiation to the pelvic, abdominal para-aortic, and pulmonary areas prior to whole-body exposure.

In summary, 200 r whole-body x-irradiation seemed to increase the bleeding tendency in some of the patients; however, it did not cause alarming accidents.

Infection complicated the postradiation period only in *case 34*. This 55-year-old patient had lesions in the lungs, ilium, 12th rib, and 12th thoracic vertebra. Biopsy yielded a histologic diagnosis of undifferentiated malignant tumor, and autopsy revealed widely disseminated Hodgkin's disease. Several courses of limited field roentgen therapy provided temporary amelioration, in January 1956 whole-body x-irradiation was administered. Daily low-grade fever appeared on the 24th postradiation day, and antibiotic treatment with penicillin and streptomycin and, later, achromycin was started. A profound pancytopenia necessitated a series of whole-blood transfusions. Several gluteal abscesses and ulcerating lesions involving gingiva and hard palate developed; on culture they yielded beta-hemolytic *Micrococcus pyogenes*, var. *aureus*, resistant to achromycin. Therefore, the previous antibiotics were replaced by erythromycin, and gradual improvement took place. The patient became afebrile on the 51st day postradiation, the infectious lesions began to heal, and the leukocyte count rose to 2,300 from a previous minimum of 100.

Life expectancy. All 30 patients of the final 200-r group died within 20 months; mean survival time was 4.4 months. Because of the wide individual variability in the group as to age as well as to tumor type (table 1), and because of lack of an untreated control series of similar composition, it was difficult to assess the

extent to which radiation had affected the life expectancy of the patients; however some estimate was possible. The 12 cases of bronchogenic carcinoma, representing a relatively uniform population, were separated from the rest of the 200-r series and were compared with data available in the literature. In these 12 patients the carcinoma was too advanced to be operable or to be suitable for radical radiotherapy; even palliative irradiation in its ordinary form was not considered promising. In 3 instances diagnosis was based on both roentgenologic demonstration of lung or mediastinal abnormalities, consistent with bronchogenic carcinoma, and on biopsy reports of malignancy from either the chest wall or a supraclavicular lymph node; in the remaining cases diagnosis was confirmed by bronchoscopic biopsy in 2, by biopsy at thoracotomy in 3, and by histologic examination at autopsy in 4. Mean survival time after 200 r whole-body x-irradiation in these 12 cases was 3.5 months. Rienhoff (11) reported a life expectancy of "approximately 5 months" for a group of 344 patients, "many" of whom had received local radiotherapy after irremovable tumors had been found at chest exploration. Watson (12) found in 295 untreated lung cancer patients a mean survival time of 3.1 months. In figure 10, the survival distribution of the present series of

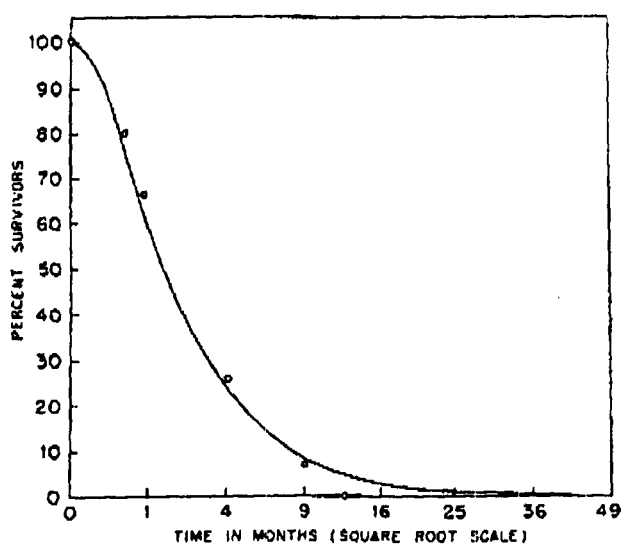

FIGURE 10

Life expectancy of advanced lung cancer patients. The curve represents Watson's untreated series of 295 cases (ref. 12, fig. 1), while the open circles are derived from 12 lung cancer patients exposed to 200 r whole-body irradiation.

12 lung cancer patients was compared with that of Watson's untreated group (ref. 12, fig. 1). What interpretation should be given to the surprising coincidence between the two sets of data in figure 10? Obviously, life expectancy was determined largely by the state of the malignancy, and therefore by the standard for selection of cases. Under the reasonable assumption that the present series showed at least as advanced a state of disease as Watson's untreated series, the conclusion would be reached that *200-r whole-body x-irradiation either did not affect at all the life span of the patients, or might even have caused a slight prolongation.*

Any comparison of survival times between the final 200-r group and the exploratory groups was meaningless, obviously, since the standard for selection of patients shifted markedly during evolution of this study as described under "Method."

2. Brief survey of the exploratory phases

The first exploratory group consisted of 199 patients exposed to doses ranging from 15 to 75 r. Treatment was well tolerated in all cases. With the exception of one patient, who experienced a brief episode of nausea on the day of irradiation, no member of the group reported complaints characteristic of the above-described early reactions. Since during this phase, as described under "Method," whole-body irradiation was used only as an adjuvant to established types of therapy, a detailed hematologic analysis was not performed. Gross examination of the data indicated irregular fluctuations probably caused by disease and conventional treatments. There seemed to be no significant enhancement of life expectancy, as revealed by the following considerations: The first exploratory phase ended in the spring of 1953. Review of the hospital records, at 3 years after conclusion of the phase, showed that 70 percent of the patients were dead, or presumed dead, while 30 percent were living. Thus, at the time of survey, approximately one-third of the group were alive between 3 and 5 years after whole-body exposure. Such a survival rate was not believed significantly greater than that expected without whole-body irradiation as an adjuvant, as judged from clinical experience.

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The next group consisted of 18 patients exposed to 100 r. Results were essentially the same as in the preceding series; however, there were some hematologic changes definitely induced by whole-body x-irradiation during the initial observation period (table V). For statistical evaluation, the group means of the measurements on each postradiation day were compared with the corresponding values determined 2 days prior to exposure, and Student's t-test was applied to the differences. This procedure yielded the following result: neither total white blood cell counts nor platelet counts showed any radiation effect, while a drop in lymphocytes occurred which became significant on the 0.01 level after the second postradiation day.

The third exploratory group consisted of 17 patients exposed to doses as follows: 125 r, 5 cases; 150 r, 6 cases; 175 r, 1 case; and 200 r, 5 cases. Since the number of patients for each dose level was too small for analysis, the 125 r, the 150 r, and 175 r cases were pooled; the five 200 r cases were excluded from the pool since their data had been partially considered in the preceding section. The following observations were made on the 12 pooled 125- to 175-r cases: Early reactions were easily recognized; 7 patients vomited and 4 did not, while no record was available in the remaining case. Definite hematologic changes occurred during the initial 2-week observation period (table VI). Statistical evaluation with the above-described procedure showed a drop in total leukocyte count which became significant on the 0.01 level after the seventh postradiation day, a decline in lymphocytes which became significant after the fourth postradiation day, and no change in thrombocytes. Clinically significant complications, as described for the final 200-r group, were not encountered.

TABLE V

Effect of 100 r whole-body x-irradiation on the number of white blood cells, lymphocytes, and platelets in 1 mm.³ of blood. Means and standard deviations obtained from a group of 18 patients have been tabulated.

Time (days)	WBC (thousands/mm.³)		Lymphocytes (thousands/mm.³)		Platelets (thousands/mm.³)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Pre-radiation						
1	7.19	3.02	1.47	.74	202	80
2	7.49	3.08	1.45	.63	196	79
3	8.18	2.71	1.50	.64	188	51
Irradiation						
0	7.59	2.16	1.16	.52	203	82
Postradiation						
1	7.94	2.52	1.09	.40	—	—
2	7.41	2.47	.86	.31	187	80
3	7.54	2.94	.88	.39	213	36
4	7.62	2.96	.95	.46	196	92
5	7.73	3.21	.91	.43	223	58
6	7.69	3.96	.79	.34	211	58
7	6.79	2.72	.73	.37	246	34
8	7.49	4.18	.84	.37	171	43
9	7.05	2.69	.76	.32	223	91
10	6.91	2.74	.85	.41	188	31

To obtain a gross estimate of the dose dependency of the hematologic changes, the group means in percent of their preradiation level were represented graphically (figs. 11 and 12). This procedure showed that the fall in total white blood cells became more pronounced with increasing dose (fig. 11), while the reduction in lymphocytes was practically independent of dose (fig. 12).

3. Double exposures

Eight patients, who seemed to have improved after the first whole-body irradiation, received a second treatment when deterioration again began; the interval between the two exposures varied from 77 to 187 days. The following dose combinations were used: 50 + 50 r (1 case), 100 + 150 r (3 cases), 125 + 150 r (1 case), 150 + 150 r (1 case), 175 + 175 r (1 case), and 125 + 200 r (1 case). The number of patients in this series was too small to allow definite conclusions. The following impression was gained, however: responses to the second dose seemed more pronounced than those following the first. This apparently was true for the initial reactions—fatigue, anorexia, nausea, and vomiting—as well as for the delayed bone-marrow depression. Following the first dose the instances of clinically significant leukopenia, thrombocytopenia, and anemia, as defined above, were as follows: 0, 2, and 5, respectively; following the second dose they were 3, 5, and 5, respectively. Since the second dose was larger than the first in 5 of these patients, the greater response following re-exposure might be explained on this basis alone. However, two impressions seemed to indicate a true increase in general radiosensitivity persisting even several months after application of the initial dose. First, enhanced reactions occurred also in those 3 patients who had received a second dose that was equal to the first in size; and second, aggravation of reactions seemed indicated when responses

TABLE VI

Effect of 125-175 r whole-body x-irradiation on the number of white blood cells, lymphocytes, and platelets in 1 mm.³ of blood. Means and standard deviations obtained from a group of 12 patients have been tabulated.

Time (days)	WBC (thousands/mm.³)		Lymphocytes (thousands/mm.³)		Platelets (thousands/mm.³)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Pre-radiation						
1	8.68	2.35	1.46	.50	198	65
2	7.95	1.79	1.30	.41	228	77
3	8.76	2.32	1.39	.32	274	87
Irradiation						
0	8.11	1.84	1.39	.32	237	97
Postradiation						
1	8.50	2.30	1.11	.38	—	—
2	8.54	2.81	.94	.24	231	78
3	7.27	1.36	1.00	.29	192	70
4	7.07	1.68	.83	.24	262	96
5	7.10	1.91	.90	.41	180	80
6	6.63	1.62	.92	.39	—	—
7	6.41	1.55	.86	.30	204	76
8	6.05	1.13	.83	.29	—	—
9	6.02	1.24	.79	.38	202	83
10	6.03	1.17	.79	.24	191	52

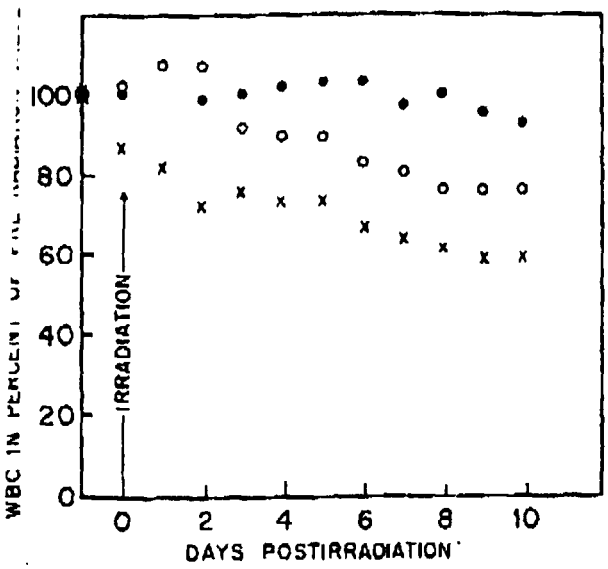

FIGURE 11

*Dose dependency of the effect of whole-body irradiation on the total white blood cell count. he markings denote the following: **dots**, statistical eans derived from 18 patients exposed to 100 r; **pen circles**, statistical means derived from 12 atients exposed to doses between 125 and 175 r; and **rosses**, statistical means derived from 30 patients xposed to 200 r.*

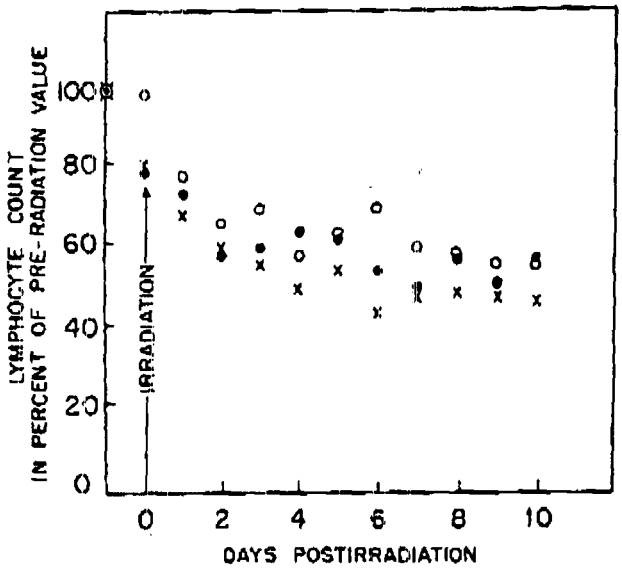

FIGURE 12

*Dose dependency of the effect of whole-body x-irradiation on the lymphocyte count. The markings denote the following: **dots**, statistical means derived from 18 patients exposed to 100 r; **open circles**, statistical means derived from 12 patients exposed to doses between 125 and 175 r; and **crosses**, statistical means derived from 30 patients exposed to 200 r.*

o the second dose were compared with those ppearing in patients who had received a single xposure of corresponding size. Loeffler (13) nade similar observations and explained them s a reduction of the body's capacity to repair adiation-induced cell damage.

DISCUSSION

Biologic actions of ionizing radiation become nore and more objectives of two different ields. The first, radiotherapy, utilizes such ctions for curing disease in human patients; he second, radiobiology, attempts to discover and explain these actions by experimental neans. The two fields of endeavor have accumulated a wealth of information which, when properly exchanged, may prove fruitful and stimulating to each other. To foster such an exchange, the radiotherapist has to record observations that are often clinically of little significance, and to present them in a form that enables comparison with findings obtained from accidental irradiation of healthy human beings and from animal studies. The present report attempts a step in this direction.

On the one hand, the data of this report are well suited for comparison because of the exposure conditions under which they were obtained. Lateral irradiation by two opposing fields produces a rather homogeneous dose distribution through the body (9); thereby, it approximates conditions existing during the unilateral exposure of small laboratory animals to radiation of comparable penetration and also those during human exposure to radiation of much higher penetration such as produced by cobalt-60, cesium-137, and nuclear explosions. On the other hand, the present data are limited in their general radiobiologic value because of the unpredictable distortion superimposed by disease; therefore, great caution must be exercised in drawing far-reaching conclusions. Although a thorough comparative analysis of the data lies beyond the scope of the present report, a general impression may be given. Close similarity seems to prevail between the systemic effects produced in cancer patients by whole-body x-irradiation and those caused in healthy human beings by nuclear explosions. Both type and time-course of the biologic

reactions appear to agree well; however, there may exist a difference in degree. Understandably, the terminal cancer patient with his spontaneous tendency toward vomiting, bone-marrow depression, and hemorrhage may be expected to have an increased radiosensitivity with respect to induction of these symptoms. This restriction should be applied to the summarizing statements of the next paragraph.

Systemic and clinical effects induced by whole-body x-irradiation occur essentially in two phases that may demand special medical attention. The first one, the initial reaction, is characterized by fatigue, anorexia, nausea, and vomiting. In typical cases, it begins approximately 2 hours after exposure and subsides 24 hours later. As shown by Court Brown (14), a strong psychologic component may frequently be involved. The second phase, a more or less pronounced bone-marrow depression, is characterized by a tendency toward bleeding, infection, and pancytopenia. In typical cases, it becomes significant clinically 3 to 4 weeks postirradiation and begins to subside 6 to 8 weeks after exposure. Generally, doses of 100 r or lower are subthreshold and will not produce these reactions. In the dose range between 125 and 175 r the two phases begin to appear in about 50 percent of the cases; however, the reactions are too mild to demand countermeasures other than psychologic reassurance. At 200 r, the two phases are clearly recognizable in about 80 percent of the cases; and reactions are sufficiently severe to require clinical treatment in about 10 percent of the patients. Thus the threshold dose, beyond which in a small percentage of patients serious complications begin to appear, lies somewhere between 150 and 200 r.

SUMMARY

A series of 263 cancer patients received whole-body irradiation with doses ranging from 15 to 200 r. Critical evaluation of the procedure as a therapeutic tool was excluded from the report; its scope was limited essentially to acute and subacute effects, so far as they were systemic in nature. These effects—predominantly nausea, vomiting, and bone-marrow depression—were practically absent below 100 r; they became noticeable between 125 and 175 r; and they developed into complications requiring clinical treatment in 10 percent of the patients at 200 r.

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