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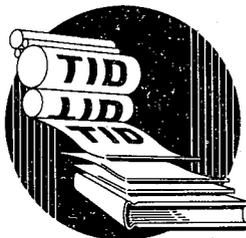
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**HEMATOLOGICAL EFFECTS OF IONIZING
RADIATIONS VII.**

By
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April 1, 1949 - February 28, 1950

University of California
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HEMATOLOGICAL EFFECTS OF IONIZING RADIATIONS VII*†

By B. V. A. Low-Beer and Paul M. Aggeler‡

INTRODUCTION

The following paper is a report of the progress made in the study of hematological effects of total-body irradiation during the period from Apr. 1, 1949, to Feb. 28, 1950. The purpose of this investigation is the observation of morphological changes which become evident in the peripheral blood of patients following exposure to therapeutic doses of ionizing radiations. The project was started in October 1942, and the first comprehensive report was published in February 1948 by the Argonne National Laboratory (Report CH-3863, Part I, by B. V. A. Low-Beer and R. S. Stone). That report will be included in Volume XX of Division IV of the National Nuclear Energy Series (McGraw-Hill Book Company, Inc., publisher). The report, which covers the period to June 30, 1946, consists in studies of 29 patients who were treated by total-body exposures to X rays generated by 100, 200, and 1000 kv potentials. The following reports have been published subsequently:

- B. V. A. Low-Beer, UCRL-41, Part II, covering the period July 1, 1946, to Dec. 31, 1947.
- B. V. A. Low-Beer, UCRL-98, Part III, covering the period Jan. 1, 1948, to Mar. 31, 1948.
- B. V. A. Low-Beer, UCRL-157, Part IV, covering the period Apr. 1, 1948, to June 30, 1948.
- B. V. A. Low-Beer, UCRL-193, Part V, covering the period July 1, 1948, to Sept. 30, 1948.
- B. V. A. Low-Beer, UCRL-332, Part VI, covering the period Jan. 1, 1949, to Mar. 31, 1949.

In addition to the 29 patients whose reports are given in CH-3863, our studies include three patients treated with 100-kv generated X rays between July 1946 and January 1947, 21 patients treated with radiophosphorus administered intravenously between September 1946 and May 1948, and 33 patients treated with radioiodine administered orally between October 1946 and February 1950.

In order to be included in the study patients must have had normal blood counts prior to treatment and must have been available for long-term follow-up. Methods of hematological investigation and criteria for evaluation were set forth in Report CH-3863. Pretreatment values were established for all elements of the blood, and examinations were repeated at definite planned intervals after treatment. The following deviations from pretreatment levels were arbitrarily designated as significant: Hemoglobin and erythrocyte count ± 15 per cent; white blood cell count, polymorphonuclear leukocyte count, and lymphocyte count ± 40 per cent; monocyte count ± 100 per cent. While previous reports include observations on 66 patients, actually 87 patients were studied for various lengths of time, but the data on 19 of these patients were not considered complete enough for inclusion in previous reports. The current report deals with certain aspects of the treatment and observation of all 87 patients.

SCOPE OF PRESENT REPORT

With respect to patients who received total-body X-ray therapy or intravenous radiophosphorus treatment the following are evaluated:

1. Additional blood counts on patients still under observation.
2. All data relating to the lobe index since the beginning of the project in October 1942.

*Work performed under Contract No. AT-11-1-Gen-10.

†Previous reports on this subject, I-VI, are listed in the introduction.

‡With the technical assistance of Dorothy L. Corey and Norman E. Scofield.

3. Evaluation of platelet counts.
4. Analysis of dose-effect relations.

With regard to the patients who received radioiodine treatment, the following studies have been made:

1. Analysis of all hematologic data collected to date.
2. Studies on blood clearance and urinary excretion of I¹³¹.
3. Analysis of dose-effect relations.

HEMATOLOGICAL EFFECTS OF X RAYS

Patients Treated with X Rays

During the current reporting period (April 1949 to February 1950) six patients of the original group treated with total-body X-ray irradiation were followed.

Table 1 shows the physical factors and the treatment and observation periods for each of the six patients.

Table 1

Case	Kv	No. of Exp.	Duration of Rx, days	r (skin) per Rx	Total-body exposure, r (skin)	Whole-body dose, r (tissue)	Duration of obs., days
9	200	14	16	20	300	201	2309
10	200	15	17	20	307	206	2337
11	200	15	17	20	300	201	2436
22	1000	15	18	20	300	204	1746
30	100	30	35	10	300	48	1232
31	100	30	35	10	300	48	1234

Case 9

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 13.0 g, the erythrocyte count was 5,000,000/cu mm, and the color index was 0.90. For the first 480 days the hemoglobin fluctuated between 12.0 and 13.0 g. Between 480 and 720 days it gradually rose to a level between 15.0 and 16.0 g and remained at this level until 1175 days, when it gradually began to drop again. Between 2004 days and the date of last observation on 2309 days it fluctuated between 12.5 and 15.1 g.

For the first 320 days the erythrocyte count fluctuated between 4,500,000 and 5,000,000/cu mm. Between the 320th and 750th days it varied between 5,000,000 and 5,500,000/cu mm. Between the 750th and 1670th days it remained between 4,000,000 and 4,500,000/cu mm. Between the 1670th day and the date of the last observation (2309th day) it ranged between 4,000,000 and 5,500,000/cu mm, with a tendency of the more recent counts to the region between 4,500,000 and 5,000,000/cu mm.

Slight anisocytosis, macrocytosis, and polychromatophilia were noted between the 750th and 1150th days.

There was no significant change in the color index from the pretreatment level of 0.90 until the 720th day, when it rose to 1.07 owing to elevation of the hemoglobin level without a compensatory rise in the erythrocyte count. Between that day and the 1600th day it remained elevated to between 1.23 and 1.34, in part because of continued elevation of the hemoglobin level and in part because of a reduction in the erythrocyte count. Since the 1600th day it has returned to the pretreatment level, concomitant with similar changes in the hemoglobin concentration and the erythrocyte count. The last count recorded on Aug. 24, 1949, showed hemoglobin 12.5 g, erythrocyte count 4,800,000/cu mm, and color index 0.89.

Leukocytes. The pretreatment total leukocyte count was in the region of 8000/cu mm, with a

normal differential count. During the first 2 days of treatment reductions to as low as 3500/cu mm occurred. The approximate pretreatment level was then maintained until the 38th day, with the exception of an elevation to 14,000/cu mm on the 9th day. Between the 38th and 233d days most of the counts recorded were between 4000 and 5000/cu mm. Between the 233d and the 646th days most of the counts were between 6000 and 9000/cu mm. Between the 646th and 872d days almost all the counts were in the region of 4000/cu mm. Since the 872d day the counts have varied between 4000 and 8000/cu mm, with the majority in the past year in the region of 5000/cu mm.

The neutrophilic leukocytes showed a marked decrease during the first 2 days of treatment, concomitant with the decrease in total leukocytes. During the first 300 days reductions in the percentage of neutrophils and lymphocytes and elevations in the percentage of monocytes accompanied reductions in the total leukocyte count. The decrease in lymphocytes preceded, and was more pronounced than, the decrease in neutrophils. Between the 300th and 600th days the differential count was characterized by a relatively greater reduction in neutrophils than in lymphocytes and by persistent elevation of the monocyte count. Between the 600th and 1600th days there was a gradual return to the normal pretreatment values. Since that time the normal values have been maintained.

Platelets. The platelet count varied between 330,000 and 490,000/cu mm during the first 600 days. Between the 600th and the 1600th days the counts varied from 200,000 to 340,000/cu mm. Between the 1600th day and the last count on the 2309th day the counts varied between 150,000 and 290,000/cu mm. These counts are all within the normal range standards of the technicians employed. The differences observed between the various periods are attributed to differences in technique employed by the different technicians.

Case 10

Hemoglobin and Erythrocytes. Pretreatment hemoglobin value was 12.4 g, erythrocyte count was 4,400,000/cu mm, and the color index was 0.97. During the first 11 days there was a gradual drop in the hemoglobin level to 11.0 g and during the next 4 days a gradual elevation to 13.0 g, which was maintained until 70 days, when it again gradually dropped, reaching its lowest point of 9.9 g on the 182d day. It then rose to 13.8 g on the 512th day. Since the 512th day it has fluctuated between 12.8 and 14.2 g.

On the 2d day the erythrocyte count rose to an average level of 5,000,000/cu mm and remained at this level during the first 30 days. It then fluctuated between 4,000,000 and 5,000,000/cu mm until the 400th day. Since then it has remained at a general average level of 5,000,000/cu mm.

Slight anisocytosis, poikilocytosis, polychromatophilia, macrocytosis, and basophilic stippling were noted between the 715th and 1180th days.

No significant change in the color index was noted except a slight decrease between the 5th and 10th days, reaching a value of 0.82 on the 10th day because of a decrease in the hemoglobin level without a similar reduction in the erythrocyte count.

The last count recorded on this patient on Nov. 1, 1949 (the 2337th day), showed hemoglobin 12.8 g, erythrocyte count 4,820,000/cu mm, and color index 0.87.

Leukocytes. The pretreatment total leukocyte count was in the region of 9000/cu mm, with a normal differential count. During the first 30 days the total count ranged between 7000 and 18,200/cu mm. Between the 38th and 59th days the counts ranged from 3500 to 7000/cu mm. From the 59th to the 568th days almost all the counts were between 10,000 and 12,000/cu mm. Since the 568th day most of the counts have ranged between 4500 and 9500/cu mm, although there have been sporadic elevations to as high as 14,000/cu mm. Since the 1714th day no such elevations have occurred.

In general, the elevations of the total leukocyte count were due mainly to elevations in the lymphocyte and monocyte levels and, to a lesser extent, to elevations in the numbers of neutrophils. On the other hand, the decreases in the total leukocyte count were due principally to reductions in the numbers of neutrophils. Since the 80th day of observation the differential counts have been essentially normal.

Platelets. In consideration of the different normal ranges of the different technicians, the platelet counts remained normal except for a persistent thrombocytopenia of 70,000 to 110,000/cu mm noted between the 869th and 1180th days.

Case 11

Hemoglobin and Erythrocytes. The pretreatment hemoglobin level was 13.2 g, the erythrocyte count was 4,650,000/cu mm, and the color index was 0.98. The hemoglobin level remained unchanged until the 100th day. It then dropped slightly to a level of 12.0 to 12.5 g until the 400th day. Between the 400th and 600th days a gradual elevation to a level of 14.2 to 15.5 g occurred. This level was maintained until the 2100th day. Since then an even higher level of 15.0 to 17.4 g has persisted. A general average level of approximately 5,000,000 erythrocytes per cubic millimeter was maintained until the 700th day, with occasional depressions to as low as 4,000,000/cu mm and elevations to as high as 5,700,000/cu mm. Between the 700th and 2000th days the general average of the counts was in the region of 4,500,000/cu mm. Since the 2000th day the counts have been only slightly under 5,000,000/cu mm.

Slight anisocytosis and macrocytosis were noted between the 700th and 1100th days.

The color index rose between the 500th and 600th days from the pretreatment value of 0.98 to 1.15, and since that time it has varied between 1.08 and 1.20. This change was due almost entirely to an increase in the hemoglobin concentration. The last count recorded on this patient on Oct. 26, 1949, showed hemoglobin 16.1 g, erythrocyte count 5,050,000/cu mm, and color index 1.11.

Leukocytes. The pretreatment total leukocyte count was in the region of 9000/cu mm with a normal differential count. It remained at this level except for two periods, one between the 30th and 70th days and the other between the 580th and 800th days, when counts ranging from 3400 to 5500/cu mm were recorded. During the first of these periods the reduction was due mainly to neutropenia, and during the second period it was due to lymphopenia and monocytopenia. Since the 800th day the differential counts have been normal. It should be noted that throughout the entire period of observation from the 2d day onward, and particularly during the first 800 days, there was a tendency toward a greater absolute number of neutrophils and a lesser absolute number of lymphocytes than in the pretreatment period. There was also an increase in the absolute number of monocytes during the first 400 days.

Platelets. The platelet counts were within the respective normal ranges of the various technicians throughout the entire period of observation.

Case 22

Hemoglobin and Erythrocytes. The pretreatment hemoglobin level was 12.1 g, the erythrocyte count was 4,720,000/cu mm, and the color index was 0.94. There has been no persistent trend either toward elevation or reduction of the hemoglobin concentration in this patient. Sporadic reductions to the region of 10.0 to 11.0 g occurred on the 10th, 38th, 1613th, 1627th, and 1716th days. Elevations to as high as 14.5 g occurred irregularly.

The erythrocyte count ranged between 4,500,000 and 5,500,000/cu mm during the first 22 days, and since that time it has ranged between 3,600,000 and 4,500,000/cu mm.

Slight anisocytosis was noted throughout the entire period of observation.

No persistent change in the color index occurred.

The last count recorded on this patient on Sept. 2, 1949, showed hemoglobin 12.1 g, erythrocyte count 4,220,000/cu mm, and color index 0.99.

Leukocytes. The pretreatment total leukocyte count was in the region of 14,000/cu mm, with the following differential count: neutrophils 78 per cent, eosinophils 1 per cent, lymphocytes 15 per cent, and monocytes 6 per cent.

The level of the total leukocyte count was maintained until the 13th day, when a gradual reduction set in. The maximum reduction, to a count of 5000/cu mm occurred on the 45th day. Following this, the count gradually rose to a region of 9000 to 12,000/cu mm by the 120th day. This level was maintained until the 1560th day. Since that time almost all the counts have been in the region of 5500 to 9000/cu mm. The leukopenia which occurred between the 13th and 120th days was due almost entirely to lymphopenia, although a substantial reduction in monocytes also occurred between the 22d and 87th days.

The relative increase in neutrophils and decrease in lymphocytes observed in the pretreatment

period persisted throughout the entire period of observation despite the changes which have occurred in the total leukocyte count. The last count on this patient on Sept. 2, 1949, showed the total leukocyte count to be 8500/cu mm and the differential count to be neutrophils 74 per cent, eosinophils 3 per cent, basophils 1 per cent, lymphocytes 13 per cent, and monocytes 7 per cent.

Platelets. The platelet counts were within the respective normal ranges of the various technicians throughout the entire period of observation except for occasional slight nonpersistent reductions whose significance cannot be evaluated.

Case 30

Hemoglobin and Erythrocytes. The pretreatment hemoglobin level was 13.8 g, the erythrocyte count was 4,840,000/cu mm, and the color index was 0.98. No significant change occurred in these values during the entire period of observation, and no abnormalities in the erythrocyte count were noted. The last count on this patient on Dec. 14, 1949, showed hemoglobin 13.1 g, erythrocyte count 4,830,000/cu mm, and color index 0.94.

Leukocytes. The pretreatment total leukocyte count was in the region of 9000/cu mm, with a normal differential count. Between the 21st and 94th days a slight reduction, with total counts in the region of 6000 to 8000/cu mm, occurred. This was due almost entirely to reduction in the absolute number of lymphocytes. Since the 94th day the total leukocyte count and the differential count have remained at their pretreatment levels.

Platelets. The platelet counts remained within the respective normal ranges of the various technicians throughout the entire period of observation.

Case 31

Hemoglobin and Erythrocytes. The pretreatment hemoglobin level was 15.7 g, the erythrocyte count was 5,490,000/cu mm, and the color index was 0.98. No significant change occurred in these values during the entire period of observation, and no abnormalities in the erythrocyte count were noted. The last count on this patient on Jan. 30, 1950, showed hemoglobin 15.7 g, erythrocyte count 5,860,000/cu mm, and color index 0.92.

Leukocytes. The pretreatment total leukocyte count was in the region of 10,000/cu mm. The differential count showed neutrophils 46 to 58.5 per cent, eosinophils 5.5 to 13.0 per cent, basophils 0.5 to 10 per cent, lymphocytes 29.5 to 38 per cent, and monocytes 5.5 to 7.5 per cent. Throughout the entire period of observation the total count varied between 7000 and 11,000/cu mm without a persistent trend in either direction. Between the 10th and 268th days the percentage of neutrophils tended to range between 55 and 70 per cent and the lymphocytes between 20 and 35 per cent. Since then the relative proportions of these cells has shifted to a region of 35 to 60 per cent neutrophils and 30 to 50 per cent lymphocytes. The percentage of eosinophils and monocytes has remained unchanged.

Platelets. The platelet counts remained within the respective normal ranges of the various technicians throughout the entire period of observation.

Summary

1. Six patients who received total-body irradiation are still under observation and have been followed for periods varying from 1232 to 2309 days since treatment was started.
2. Changes in the erythrocyte count, hemoglobin concentration, color index, or platelet count which occurred following irradiation have not persisted. During the past year these values have all been in the region of the pretreatment values (see Tables 2 and 3).
3. The following persisting changes in the leukocytes have been observed in individual patients:
 - (a) a tendency toward a leukopenia with no significant change in the differential count (patient 9);
 - (b) a tendency toward a greater absolute number of neutrophils and a lesser absolute number of lymphocytes without change in the total leukocyte count (patient 11);
 - (c) a reduction from a slight pretreatment leukocytosis to a normal leukocyte count without change in the differential count (patient 22);
 - and (d) a shift to a greater absolute number of lymphocytes and a lesser absolute number of neutrophils without change in the total leukocyte count (patient 31).

Table 2—Individual Values for Each Patient

Patient	Days from Rx	Pretreatment			Last observation		
		RBC	Hb, %*	C.I.	RBC	Hb, %*	C.I.
9†	2309	5.00	90	0.90	4.80	86	0.89
10†	2337	4.40	85	0.97	4.82	88	0.87
11†	2436	4.65	91	0.98	5.40	114	1.06
22	1746	4.72	88	0.94	4.22	83	0.99
30	1232	4.84	95	0.98	4.83	90	0.94
31	1234	4.97	100	1.01	5.86	108	0.92

*Based on 14.5 g equals 100 per cent.

†On patients 9, 10, and 11 the hemoglobin values which were originally reported on the basis of 13.8 g equaling 100 per cent hemoglobin have been corrected to the present value of 14.5 g.

Table 3—Averaged Values for the 6 Patients

	Pretreatment	Last observation
Erythrocyte count, cu mm	4.76	4.99
Hemoglobin, %	91.5	95
Color Index	0.96	0.95

HEMATOLOGICAL EFFECTS OF RADIOPHOSPHORUS

Patients Treated with Radiophosphorus

During the current reporting period (April 1949 to February 1950) 12 patients of the original group treated with radiophosphorus were studied hematologically.

Table 4 shows the treatment factors and observation periods of these 12 patients.

Case 35

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 13.9 g, the erythrocyte count was 4,460,000/cu mm, and the color index 1.08. The hemoglobin value remained in the range of 13.5 to 15.2 g for the first 800 days. Since then it has ranged between 11.3 and 12.5 g.

There was no significant variation in the erythrocyte count throughout the entire period of observation.

Since the 800th day there has been a lowering of the color index which is due to the reduction in the hemoglobin concentration without a concomitant reduction in the erythrocyte count.

No significant alterations in the erythrocyte morphology were noted.

The most recent count on this patient on Jan. 11, 1950, showed hemoglobin 12.5 g, erythrocyte count 4,790,000, and color index 0.90.

Leukocytes. The pretreatment total leukocyte count was in the region of 7000/cu mm. The count was reduced to between 4000 and 6000/cu mm between the 28th and 98th days. A similar reduction occurred between the 700th and 1000th days. At all other times the count has been at or near its pretreatment value. The reductions in the total count were due both to neutropenia and to lymphopenia.

Platelets. A slight reduction in the platelet count occurred between the 40th and 70th days.

Table 4—Treatment with $\text{Na}_2\text{HP}^{32}\text{O}_4$ Intravenously

Patient	No. of admin.	Duration of treatment	Total, mc	Fractionation interval, Millicuries - days	Time of observation, days
35	4	21	8.00	mc 2 - 2 - 1 - 3 Days 7 - 7 - 7	1108
36	4	20	6.70	mc 2 - 2 - 2 - 0.7 Days 6 - 7 - 7	1020
39	4	41	8.00	mc 2 - 2 - 2 - 2 Days 7 - 7 - 27	874
41	3	39	6.00	mc 2 - 2 - 2 Days 32 - 7	1126
42	4	40	6.82	mc 2 - 2 - 2 - 8.2 Days 26 - 7 - 7	1120
45	4	20	8.00	mc 2 - 2 - 2 - 2 Days 7 - 7 - 6	852
46	4	20	8.02	mc 2 - 2 - 2 - 2 Days 7 - 6 - 7	1008
47	4	22	8.00	mc 2 - 2 - 2 - 2 Days 8 - 7 - 7	808
50	4	21	8.00	mc 2 - 2 - 2 - 2 Days 7 - 7 - 7	602
52	4	21	8.00	mc 2 - 2 - 2 - 2 Days 7 - 9 - 7	634
53	3	14	6.00	mc 2 - 2 - 2 Days 7 - 7	662
54	3	14	6.00	mc 2 - 2 - 2 Days 7 - 7	631

Case 36

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 11.4 g, the erythrocyte count was 5,130,000/cu mm, and the color index was 0.77. Between the 30th and 90th days the hemoglobin remained at a level of 10.4 to 10.7 g. By the 110th day it had risen to 12.0 g, and thereafter it was maintained at a level of 12.0 to 14.2 g.

The erythrocyte count began to drop on the 6th day and reached its lowest point, with a count of 3,830,000/cu mm, on the 54th day. Thereafter it gradually rose to a level between 4,500,000 and 5,000,000/cu mm by the 110th day. Since then this level, which is slightly below the pretreatment level, has been maintained.

As a consequence of the above changes, the color index rose on the 110th day to 0.87, and since that date it has ranged between 0.87 and 1.03.

The most recent count on this patient on Oct. 20, 1950, showed hemoglobin 13.8 g, erythrocyte count 4,590,000, and color index 1.03.

Leukocytes. The pretreatment total leukocyte count was in the region of 10,000/cu mm, with a normal differential count. The total count began to drop on the 20th day and reached its lowest point of 2400/cu mm on the 54th day. It then began to rise, and it reached a level of 7250/cu mm by the 97th day. Since then it has ranged between 7250 and 9300/cu mm. Even at the height of the leukopenia there was little change in the differential count.

Platelets. There was a definite reduction in the platelet count from a level of 210,000 to 260,000/cu mm before treatment to a level of 60,000 to 90,000/cu mm between the 30th and 76th days.

Since the 76th day the platelet counts have been within the normal ranges of the various technicians.

Case 39

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 14.2 g, the erythrocyte count was 4,920,000/cu mm, and the color index was 1.00. The hemoglobin level was maintained at a level of 13.0 to 15.4 g with no persistent trend in either direction for the first 670 days. Since that time it has dropped to a level of 11.2 to 12.3 g.

There was no significant change in the erythrocyte count throughout the entire period of observation.

The color index dropped from the pretreatment value of 1.00 to values in the region of 0.90 as a consequence of the above-mentioned drop in the hemoglobin level.

The most recent count on this patient on May 17, 1949, showed hemoglobin 12.6 g, erythrocyte count 4,800,000/cu mm, and color index 0.90.

Leukocytes. The pretreatment total leukocyte count was in the region of 7500/cu mm. It began to drop on the 21st day and reached its lowest level of 2950/cu mm on the 77th day. Thereafter it gradually rose to a level of 6400/cu mm on the 246th day. It remained between 6400 and 8500/cu mm until the 700th day. Since then it has varied between 4500 and 6100/cu mm.

The pretreatment differential count was neutrophils 73 per cent, eosinophils 1 per cent, lymphocytes 18 per cent, and monocytes 7 per cent. During the first period of leukopenia there was a slight reduction in the percentage of neutrophils to the region of 60 to 65 per cent, but no significant change occurred in the remainder of the differential count. During the second period of leukopenia the neutrophils returned to the region of 50 to 65 per cent, but the percentage of lymphocytes increased to the region of 25 to 40 per cent. The last recorded count on this patient on May 17, 1949, showed total leukocyte count 4500/cu mm, differential count: neutrophils 52 per cent, eosinophils 1 per cent, lymphocytes 41 per cent, and monocytes 6 per cent.

Platelets. The platelet count remained within the normal ranges of various technicians through the period of observation.

Case 41

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 11.3 g, the erythrocyte count was 3,900,000/cu mm, and the color index was 1.00. The hemoglobin dropped to a level of 9.9 to 10.7 g between the 39th and 81st days. Thereafter it gradually rose to a high point of 14.5 g on the 483d day. Since then it has ranged between 11.2 and 13.0 g.

The erythrocyte count dropped to a low point of 3,260,000/cu mm on the 60th day and then gradually rose to the pretreatment level by the 187th day, and since then it has been maintained at that level.

Slight anisocytosis, hypochromia, polychromatophilia, and basophilic stippling were first noted at about 800 days and have persisted since then.

The color index of 1.00 was maintained throughout the period of slightly increased anemia in the immediate posttreatment period. Since then it has ranged between 1.00 and 1.18 as a consequence of the general average increase in hemoglobin which has been present since that time. The most recent count on this patient on Feb. 15, 1950, showed hemoglobin 12.6 g, erythrocyte count 3,880,000/cu mm, and color index 1.16.

Leukocytes. The pretreatment total leukocyte count was in the region of 9000/cu mm, with a differential count of neutrophils 70 per cent, eosinophils 2 per cent, basophils 0.5 per cent, lymphocytes 19.5 per cent, and monocytes 8 per cent.

During the first 561 days the count ranged from 4150 to 10,800/cu mm, with no persistent trend in either direction. Since then the counts have ranged between 4100 and 8300/cu mm, but the majority have been between 4000 and 5000/cu mm.

There was no significant change in the differential count during the first 561 days. Since then there has been a slight tendency to a lower percentage of neutrophils and a higher percentage of lymphocytes.

Platelets. A gradual reduction in the platelet count from a level of 310,000/cu mm to a low point

of 170,000/cu mm occurred between the 32d and 159th days. The same technician continued to obtain counts at this low level until her departure after the 235th day. Between the 263d and 911th days, during the tenure of the second technician, counts varying from 100,000 to 280,000/cu mm were obtained. Since the 980th day, during the tenure of the third technician, the counts have been uniformly low, ranging from 120,000 to 160,000/cu mm.

Case 42

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 10.1 g, the erythrocyte count was 4,380,000/cu mm, and the color index was 0.80. The hemoglobin rose to and remained at a general average level of 11.6 g between the 26th and 131st days. There was then a sharp drop to a value of 9.1 to 10.1 g until the 419th day. Between then and the 751st day it fluctuated between 10.4 and 12.3 g. Since the 751st day it has varied between 8.9 and 10.7 g, with a general average of about 9.7 g.

The erythrocyte counts have varied between 3,470,000 and 5,080,000/cu mm, with no persistent trend in either direction, although the general average of the counts since the 850th day has been about 4,000,000/cu mm.

Slight anisocytosis and hypochromia were first noted at about 600 days. By 900 days the hypochromia had become marked, and slight poikilocytosis and polychromatophilia were also noted. On the 1120th day marked anisocytosis and slight hypochromia were observed.

No marked or persistent changes occurred in the color index.

The most recent count on this patient on Feb. 7, 1950, showed the hemoglobin to be 9.7 g, the erythrocyte count to be 3,760,000/cu mm, and the color index to be 0.93.

Leukocytes. The pretreatment total leukocyte count was in the region of 6500/cu mm, with a normal differential count. There was a slight reduction to the level of 4100 to 5500/cu mm between the 47th and 89th days. Since then the counts have usually been in the region of 6000 to 8000/cu mm. No significant change in the differential count occurred throughout the entire period of observation.

Platelets. The platelet counts remained within the normal ranges of the various technicians throughout the entire period of observation.

Case 45

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 15.4 g, the erythrocyte count was 5,180,000/cu mm, and the color index was 1.02. The hemoglobin remained at approximately the pretreatment level for the first 260 days. Thereafter it slowly dropped to a level of 12.4 g, observed at the time the last count was taken on Sept. 6, 1949.

The erythrocyte count varied between 4,120,000 and 5,080,000/cu mm, with no significant trend in either direction.

The color index varied between 0.90 and 1.02 with no significant trend in either direction.

Leukocytes. The pretreatment total leukocyte count was in the region of 9000/cu mm with a normal differential count. A slight reduction to the region of 5000 to 7000/cu mm occurred between the 42d and 196th days. This was followed by a slight increase to the region of 10,000 to 11,000/cu mm until the 330th day. Since then the counts have varied between 6100 and 9850/cu mm.

No significant change in the differential count occurred throughout the period of observation.

Platelets. A slight reduction in the platelet count from a level of 300,000/cu mm to a level of 170,000 to 240,000/cu mm began on the 27th day and continued until the departure of the first technician on the 105th day. Subsequent counts by the succeeding technicians have been within their respective normal ranges.

Case 46

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 12.8 g, the erythrocyte count was 4,180,000/cu mm, and the color index was 1.05. During the first 410 days the hemoglobin ranged between 12.5 and 14.5 g. Thereafter it varied between 11.7 and 13.3 g.

During the first 410 days the erythrocyte count varied between 4,000,000 and 4,750,000/cu mm. Thereafter it varied between 3,500,000 and 4,500,000/cu mm.

The color index varied between 1.00 and 1.20 with no persistent trend in either direction.

The most recent count on this patient on Jan. 10, 1950, showed hemoglobin 12.3 g, erythrocyte count 4,510,000/cu mm, and color index 0.94.

Leukocytes. The pretreatment total leukocyte count was in the region of 5500/cu mm, with a normal differential count. The total counts ranged between 3500 and 7600/cu mm, with no persistent change in either direction. There was a slight reduction in the absolute number of lymphocytes between the 20th and 130th days.

Platelets. A reduction in the platelet count from a level of 260,000/cu mm to a level of 100,000 to 180,000/cu mm was noted between the 30th and 60th days. The counts have otherwise been within the normal ranges of the various technicians.

Case 47

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 15.4 g, the erythrocyte count was 4,390,000/cu mm, and the color index was 1.20. The hemoglobin varied between 14.0 and 16.2 g, the erythrocyte count between 4,300,000 and 5,000,000/cu mm, and the color index between 1.06 and 1.27 throughout the entire period of observation. There has been no trend in either direction.

The most recent count on this patient on Aug. 12, 1949, showed hemoglobin 14.5 g, erythrocyte count 4,680,000/cu mm, and color index 1.06.

Leukocytes. The pretreatment total leukocyte count was in the region of 5000/cu mm, with a normal differential count. There has been no significant variation in the total or differential counts.

Platelets. The platelet counts remained within the normal ranges of the various technicians.

Case 50

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 14.9 g, the erythrocyte count was 4,970,000/cu mm, and the color index was 1.04. The hemoglobin began to drop on the 30th day and reached its lowest point of 10.7 g on the 155th day; since then it has varied between 12.9 and 13.9 g.

The erythrocyte count began to drop concomitantly with the fall in hemoglobin and reached its lowest point of 3,330,000/cu mm at about the same time as the maximum reduction in hemoglobin occurred. Since then it has varied between 3,760,000 and 4,410,000/cu mm.

The color index has varied between 1.04 and 1.21, with the majority of the values before the 124th day falling in the region of 1.04 and 1.10 and the majority of the values since that time falling in the region of 1.10 to 1.21.

The most recent count on this patient on Oct. 27, 1949, showed hemoglobin 13.2 g, erythrocyte count 3,760,000/cu mm, and color index 1.21.

Leukocytes. The pretreatment total leukocyte count was in the region of 7000/cu mm, with a differential count of neutrophils 49 to 58 per cent, eosinophils 1.5 to 2.0 per cent, basophils 0.5 to 1.5 per cent, lymphocytes 24 to 34 per cent, and monocytes 14.5 to 15.0 per cent.

Since the 14th day the total count has been persistently lower than pretreatment levels, varying between 3800 and 6000/cu mm. Since the 270th day there has been a definite shift in the differential count, with the percentage of neutrophils varying between 34 and 40 per cent and the percentage of lymphocytes varying between 42 and 52 per cent.

Platelets. The platelet counts remained within the normal ranges of the various technicians.

Case 52

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 13.5 g, the erythrocyte count was 4,780,000, and the color index was 0.97. A slight reduction in hemoglobin values to between 11.5 and 12.5 g and of the erythrocyte count to values between 3,800,000 and 4,500,000/cu mm was observed between the 60th and 220th days. Since then the hemoglobin has been in the region of 13.5 g, and the red blood cell count has been in the region of 4,500,000/cu mm.

No significant change in the color index occurred.

Leukocytes. The pretreatment total leukocyte count was in the region of 7000/cu mm, with a normal differential count.

Since the 35th day the counts have varied between 3400 and 7000/cu mm, with the majority of the counts in the region of 4500/cu mm.

No significant change occurred in the differential count.

Platelets. There was a gradual reduction in the platelet count from a pretreatment level of 370,000/cu mm to a low point of 160,000/cu mm on the 42d day. By the 80th day the count had returned to near the pretreatment level.

Case 53

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 12.2 g, the erythrocyte count was 4,300,000/cu mm, and the color index was 0.98. A reduction in the hemoglobin to 9.9 to 11.6 g and of the red blood cell count to 3,830,000 to 3,950,000/cu mm occurred between the 44th and 72d days. Since then the pretreatment hemoglobin and erythrocyte counts have been maintained.

No significant variation in the color index occurred.

The most recent count on this patient on Jan. 18, 1950, showed hemoglobin 12.2 g, erythrocyte count 5,290,000/cu mm, and color index 0.80.

Leukocytes. The pretreatment total leukocyte count was between 7000 and 10,000/cu mm, with a normal differential count. A gradual reduction in the total count commenced on the 14th day, and since the 177th day the counts have varied between 4000 and 6000/cu mm. A decrease in the percentage of neutrophils to 43 to 46 per cent and an increase in the percentage of lymphocytes to 42 to 44 per cent occurred between the 72d and 177th day. Otherwise there has been no significant change in the differential count.

Platelets. The platelet count gradually dropped from a level of 350,000/cu mm before treatment to a low point of 160,000/cu mm on the 86th day. However, subsequent counts done by another technician were within her normal range.

Case 54

Hemoglobin and Erythrocytes. The pretreatment hemoglobin was 13.3 g, the erythrocyte count was 4,240,000/cu mm, and the color index was 1.08. The pretreatment hemoglobin and erythrocyte values were maintained until the 57th day, when the hemoglobin dropped to 11.4 g and the erythrocyte count to 3,650,000. Since that date the counts have remained in the same region.

There was no significant change in the color index.

The most recent count on this patient on Jan. 31, 1950, showed hemoglobin 11.9 g, red blood cell count 3,800,000/cu mm, and color index 1.08.

Leukocytes. The pretreatment total leukocyte count varied between 6300 to 8900/cu mm. Since the 42d day the counts have ranged between 3000 and 6200/cu mm, with the majority of the counts in the region of 5000/cu mm. A reduction in the percentage of neutrophils to 41 to 51 per cent and an increase in the percentage of lymphocytes to 38 to 49 per cent occurred between the 106th and 241st days. There has been no other persistent change in the differential count.

Platelets. No significant variation in the platelet counts occurred.

Table 5 shows the pretreatment erythrocyte count, hemoglobin concentration, and color index compared to last observation on each of the 12 P³² patients analyzed in this report.

Summary (Tables 5 and 6)

1. Twelve patients who received P³² are still under observation and have been followed for periods varying from 631 to 1085 days.
2. The following persisting changes in the hemoglobin concentration and erythrocyte count have been observed in the patients noted: (a) a slight reduction in the hemoglobin concentration and color index without change in the erythrocyte count in patients 35 and 39; (b) a slight elevation in the hemoglobin concentration and color index without change in the erythrocyte count in patient 41; (c) a moderate elevation in the hemoglobin concentration and color index and a slight reduction in the erythrocyte count in patient 36; and (d) a slight reduction in both the hemoglobin concentration and erythrocyte count without change in the color index in patients 45, 50, and 54.

Table 5—Individual Values for Each Patient

Patient	Pretreatment			Days from Rx.	Last observation		
	RBC	Hb, %*	C.I.		RBC	Hb, %	C.I.
35	4.46	96	1.08	1108	4.79	86	0.90
36	5.13	79	0.77	1020	4.59	95	1.03
39	4.92	98	1.00	874	4.80	87	0.91
41	3.90	78	1.00	1126	3.88	87	1.16
42	4.38	70	0.80	1120	3.76	67	0.93
45	5.18	106	1.02	852	4.12	92	1.12
46	4.18	88	1.05	1008	3.95	80	1.01
47	4.39	106	1.20	808	4.68	100	1.06
50	4.97	103	1.04	602	3.76	91	1.21
52	4.78	93	0.97	634	4.52	95	1.06
53	4.30	84	0.98	662	5.29	84	0.80
54	4.24	92	1.08	631	3.80	82	1.08

*Based on 14.5 g = 100 per cent.

Table 6—Averaged Values of the 12 Patients

	Pretreatment	Last observation
Erythrocyte count, cu mm	4.56	4.33
Hemoglobin, %	90	87
Color index	0.99	1.00

3. The following persisting changes in the leukocytes have been observed: (a) a slight reduction in the total leukocyte count due principally to a reduction in the absolute number of neutrophils in patients 39, 41, and 50; (b) a slight reduction in the total leukocyte count without change in the differential count in patients 52, 53, and 54.

4. There is a persisting reduction in the platelet count in case 41.

LOBE INDEX

Particular attention has been centered on the pending question of persistent changes in the lobe index of the neutrophilic leukocytes following X-ray or radiophosphorus treatment. Reference is made here to previous reports. In Report UCRL-98, February 1948, charts and tables showing the behavior of the lobe index after total-body irradiation in eight patients (19, 21, 22, 23, 26, 27, 28, and 29) were given. Examination of these records shows that an apparently significant lowering of the lobe index occurred in all but one case (patient 22). The approximate duration of lowering of the lobe index given in days after the first treatment was as follows:

Case 19	20 and 120
Case 21	40 to over 560
Case 23	17 to 80
Case 26	40 to over 350
Case 27	27 to over 360
Case 28	6 to 140
Case 29	14 to over 1950

These records include data up to June 13, 1946. Further records are available in cases 19, 21, 22, and 28. In case 19 there was a slight drop in the lobe index appearing in August 1948, almost four years after treatment; in case 21 a continued low lobe index was observed in February 1949, three years and 3 months after treatment; in case 22 the beginning of a drop occurred in May 1946 which continued and progressed until the patient was last seen in July 1948, three years and 7 months after treatment; in case 28 a significant drop in the lobe index was observed in September 1948, after a lapse from observation since November 1946. In addition, data are available on 3 other patients (30, 31, and 32) treated in September 1946. The lobe index in all three of these cases began to drop immediately after treatment. In case 32 the lowest point was reached in October 1947, and the last count recorded (August 1948) was at the pretreatment level. In cases 30 and 31 the lowest points were recorded in May 1948. Subsequent counts up to October 1948 were higher, but not so high as the pretreatment level.

Taken individually, these results are somewhat alarming, since they seem to indicate some very prolonged effects of total-body irradiation on the myeloid tissues. However, a composite graph of these cases suggests that factors other than irradiation of the patient are involved. An analysis of this graph shows that a trend toward a reduction in the lobe index began to occur in the early part of 1947 regardless of the length of time which had elapsed since the beginning of treatment in the individual cases. This trend reached its nadir in the middle of 1948 and since then has shown a slight elevation. The first question to be raised was whether these trends were due to differences between the techniques employed by three different technicians who have successively worked on this project. This did not seem to be the entire explanation for the results, since the trend began to appear in the early part of 1947, while the first technician (V. J.) was continuously employed on this work from the beginning of the project until October 1947. The second technician (A. P.) was employed between October 1947 and July 1948, and the third technician (D. L. C.) has been employed since that time.

Analysis of previously collected data showed that the average starting lobe index on the 8 cases reported was 275 and the range 222 to 306. The original counts on these patients were all done by the first technician between Oct. 25, 1944, and Nov. 13, 1945. There are no comparative data by this technician on healthy, nonirradiated subjects. A group of counts on 10 young adult normal subjects tested by the present technician in August 1949 showed an average of 140 and a range of 121 to 167. It thus appears either that the present technician's technique of counting differs from that of the first technician or that the patients studied by the first technician had abnormally high lobe indices before total-body irradiation was given. In order to further resolve these discrepancies the present technician recounted slides on 2 cases (21 and 30) previously done by herself, the 1st, or the 2d technician between March 1945 and May 1949. The results of this study showed that the present technician's present method of counting yields a lower lobe index than that originally obtained by the 1st or 2d technician or by herself in the earlier part of her employment. They also suggest that the technique of the 1st technician was constant until about January 1947. Between January and October 1947 her technique apparently changed so that she recorded increasingly lower lobe indices than she would have on the same slides in the earlier period of her employment. Further counts were made by the present technician of groups of previously counted slides as follows:

	Original count, average	Recount in Aug. 1949, average	Difference
7 random counts on 21 done by V. J. before Jan. 1947 (1st technician)	257	176	-81
10 P^{32} patients counted by V. J. between Jan. 1947 and Sept. 1947 (1st technician)	226	176	-50

	Original count, average	Recount in Aug. 1949, average	Difference
6 P ³² patients counted by A. P. (2d technician) be- tween October 1947 and July 1948	182	162	-20
16 P ³² patients counted by D. L. C. (present technician) in November 1948	199	177	-28
7 iodine cases counted by D. L. C. (present technician) between August and December 1948	204	167	-37

These data demonstrate that the first technician maintained a stable technique of counting until about January 1947, when she gradually began to record fewer lobes than she previously would have done on the same smears. The 2d technician counted lower than the 1st technician but slightly higher than the present technician. The present technician began to count in the same range as the 2d technician, but now counts much lower than her predecessors or than herself during her first few months of employment. These data appear to explain the continuing downward trend in the lobe index persisting for years after total-body irradiation. Furthermore, since there is no evidence that the first technician varied her technique until the early part of 1947, there is no reason to doubt the validity of the changes in the lobe index shown in the report of February 1948, UCRL-98, since there are no counts in that report later than June 13, 1946. In cases 19, 23, and 28 the lobe index had returned to its pretreatment level by 120, 80, and 140 days, respectively. In cases 21, 26, 27, and 29 the lobe index remained lower at the last dates shown in the report, i.e., 560, 350, 360, and 190 days. In view of the difference between the techniques of the various technicians, it would be difficult, if not impossible, to evaluate subsequent counts done on these patients where such data are available. All that can be said is that, at the present time, the lobe indices of the patients who are still being followed are, if anything, higher than the present technician's normal range. It is suggested that perhaps the lobe indices of some, if not all, of these patients were higher than normal before treatment was instituted and that they returned to and remained within the normal range following treatment in some patients (21, 26, 27, and 29) and that they reverted to the abnormally high pretreatment level in others (19, 23, and 28). In an attempt to elucidate this point, pre- and posttreatment slides of five patients were recounted with the following results:

Case		Original count by 1st technician	Present count by 3d technician
26	Pretreatment	300	203
	Posttreatment	277	184
27	Pretreatment	306	164
	Posttreatment	270	156
28	Pretreatment	238	202
	Posttreatment	207	165
29	Pretreatment	291	192
	Posttreatment	265	190
31	Pretreatment	244	204
	Posttreatment	226	198

From these data it can be seen that by the present technician's method of counting not only the pretreatment level but also the posttreatment level of the lobe index is either in the upper range of normal or is higher than the upper limit of normal. These data appear to confirm our impression that the persisting decreased lobe indices observed in patients treated with total-body irradiation several years ago are due in part to technical error and in part to real changes induced by the irradiation. The effect of the irradiation, however, was not to produce an abnormal state but, on the contrary, to induce changes toward the normal which in some cases have persisted to the present time (see Figs. 1, 2, and 3).

EVALUATION OF PLATELET COUNTS

Simple inspection of accumulated data without detailed analysis suggests a situation similar to that which pertains to the lobe index findings. The fluctuations noted in the report of February 1948, UCRL-98, are probably valid since they represent the work of a single technician (V. J.). Persisting reductions in the platelet count below pretreatment levels still observed in some patients appear in most instances to be due to differences in the technique of platelet counting of the various technicians. A review of all data relating to the platelet counts in patients treated with X ray, P^{32} , and I^{131} shows that no permanent reduction occurred except in case 41 (treated with P^{32}).

HEMATOLOGICAL EFFECTS OF I^{131}

Patients Treated with Radioiodine

Thirty-three of the patients who received radioiodine for diagnostic and therapeutic purposes⁵ were studied for hematological changes. In 25 of these patients sufficient hematological data have been accumulated to permit analysis. Twelve patients had Graves' disease, nine had carcinoma of the thyroid or metastases, one had nodular goiter, one had thyroiditis, one was euthyroid, and one was undefined.

Treatment factors, individual and total doses of radioiodine, maximum uptake of radioiodine by the thyroid gland, effective half-life, estimated dose in rep for the individual and total doses for the 25 patients who were studied are shown in Table 9. Each patient listed in Table 9 has two serial numbers. The first of these is the number under which the patient is carried in the Hematology Laboratory. The second is the patients' serial number in the Radioiodine Laboratory. All data shown in Table 9 were computed in the Radioiodine Laboratory.

The following analysis describes the hematological observations for the 25 patients.

Case: No. Hemat-55 Iod-56

Hemoglobin and Erythrocytes. The erythrocyte count and the hemoglobin values averaged 5,500,000/cu mm and 16.5 g, respectively, during the period of observation from Sept. 18, 1946, to Aug. 13, 1947. Slightly lower average values of approximately 5,400,000/cu mm erythrocytes and 16.0 g hemoglobin were observed at the beginning of the period extending from Sept. 2, 1949, to Dec. 7, 1949. There was a gradual drop in values by the end of the period to an average of approximately 4,400,000/cu mm erythrocytes and 13.0 g hemoglobin. It is impossible to state whether this change is due to the underlying metastatic cancer of the thyroid or to the radioiodine administered to one patient.

Leukocytes. The total leukocyte count ranged from 4100 to 9550/cu mm during the first period of observation. A range of 3350 to 8600/cu mm was noted during the second period of observation, except for a rise to 13,850/cu mm during a febrile episode associated with infection of the biopsy site in the pharynx during the latter part of November 1949. The leukocyte count does not appear to have been significantly altered either by the underlying disease or by radioiodine.

During both periods of observation changes in the differential count generally paralleled those observed in the total white blood cell count. No consistent changes which could be attributed to the underlying disease or to I^{131} were observed.

Table 9—Patients Treated with I^{131}

Patient		Diagnosis	Date of each treat.	Gland wt.	I^{131} , μ c	Cumulative	Max. uptake	Effect. half-life	Indiv. dose in rep in thyroid	Cumulative dose in rep in thyroid	Duration of hematomol. obs., days	
Hemat. lab.	I^{131} lab.											
55	56	Carcinoma	1-17-47		3,760	3,760						
			1-22-47		13,160	16,920						
			6-9-47		94,000	110,920						
			9-6-49		1,889	112,809						
			9-7-49		77,892	190,701						
			9-8-49		75,266	265,967						
			10-3-49		1,918	267,885						
			10-6-49		99,369	367,254						
			10-31-49		1,825	369,079						
			11-3-49		93,351	462,430						
			11-28-49		1,895	464,325						
			1-3-50		1,824	466,149						
			1-30-50		1,062	467,211						
2-28-50		911	468,122						1243			
56	105	Nodular	8-27-47	35-40	3,760	3,760	12.5					
			10-15-47	35-40	3,760	7,520	12.5					
			11-12-47		3,929	11,449	20.0				50	
62	125	Graves	11-12-47	80	7,426	7,426	75.0	3.3	4,411	4,411		
			12-15-47	65	5,922	13,348	78.0		4,221	8,632		
			3-24-48		491	13,839	55.0	10.25	1,423	10,055		
			3-25-48		5,663	19,502			16,417	26,472		
			6-2-48	15-20	447	19,949	35.0	2.5	470	26,942		
			6-4-48		1,880	21,829			1,974	28,916	807	
63	116	Carcinoma	10-16-47		3,760	3,760	21.0					
			11-20-47		47,000	50,760	11.4					
			12-9-47		1,260	52,020	16.0					
			1-28-48		902	52,922	16.0					
			2-16-48		282	53,204	26.5					
			3-29-48		3,760	56,964	20.0					
			4-16-48		188,000	244,964	?					
			7-8-48		442	245,406	4.0					
			8-4-48		2,006	297,412	4.8					
			10-18-48		2,068	249,480	5.5					
			12-14-48		1,824	251,304	4.8					394
			64	157	Graves	4-12-48	40	462	462	67.0		
4-14-48		5,597				6,059	79.0					
6-9-48	± 15	254				6,313	12.0					
1-11-49	15	489				6,802	39.7				278	
65	158	Graves	4-12-48	40-45	447	447	67.4					
			4-14-48		5,076	5,523	82.7	4.5	7,556	7,556		
			6-15-48	35-40	449	5,972	8.4					
			9-27-49		211	6,183	47.6	4.25			182	
66	138	Carcinoma	1-12-48		3,760	3,760						
			2-11-48		3,760	7,520						
			3-29-48		3,760	11,280						
			4-19-48		167,508	178,788						
			7-14-48		470	179,258						
			9-8-48		1,880	181,138						
			11-16-48		1,880	183,018						
			4-18-49		1,088	184,106						
			4-25-49		1,156	185,262						393
67	162	Carcinoma	4-26-48		3,760	3,760	19.1					
			5-14-48		101,332	105,092	?					
			7-14-48		470	105,562	4.0					
			8-11-48		1,861	107,423	5.2					
			9-7-48		1,880	109,303	6.6					
			10-13-48		1,880	111,183	4.6					
			11-30-48		1,880	113,063	?					
			3-2-49		1,876	114,939	?					
			3-11-49		1,998	116,937	6.2					
			3-18-49		1,972	118,909	5.8					
			5-24-49		1,946	120,855	6.0					393
69	179	Carcinoma	8-4-48		4,125	4,125	5.1					
			9-13-48		1,068	5,193						96

Table 9. (Continued)

Patient		Diagnosis	Date of each treat.	Gland wt.	¹³¹ I, μ c	Cumulative	Max. uptake	Effect. half-life	Indiv. dose in rep in thyroid	Cumulative dose in rep in thyroid	Duration of hematol. obs., days
Hemat. lab.	¹³¹ I lab.										
71	207	Carcinoma	11-2-48		3,008	3,008	18.5				197
			6-15-49		2,218	5,226	28.7				
			6-22-49		1,935	7,161					
			12-28-49		876	8,037					
72	208	Carcinoma	10-16-49		?						405
			11-2-48		2,961	2,961					
			2-9-49		483	3,444					
73	206	Thyroiditis	11-3-48		3,895	3,895	32.5				462
74	209	Graves	11-3-48	50	470	470	58.0				342
			11-12-48	50	7,520	7,990	66.6	6.33	11,413	11,413	
			12-27-48		314	8,304	12.6	5.0	71	11,484	
			10-11-49	N.P.	190	8,494					
75	232	?	12-20-48	60	282	282	76.5	2.2	142	142	245
			12-23-48	60	7,982	8,264	75.0		3,951	4,093	
			2-14-49	60	376	8,640	46.0	4.3	223	4,316	
			4-11-49	60	301	8,941	68.6	4.67	289	4,606	
			6-20-49	30	479	9,420	67.7	6.0	1,402	6,008	
			8-23-49	25	339	9,759	75.4	4.5	819	6,827	
76	240	Graves	1-10-49		357	357	47.4	5.9	1,798	1,798	326
			1-17-49	10	784	1,141	52.9		4,404	6,202	
			3-28-49		293	1,434	37.0	7.37	1,439	7,641	
			4-5-49	10	470	1,904	31.8	7.08	1,904	9,546	
			5-31-49		179	2,083	40.8	5.4	708	10,254	
			9-12-49	N.P.	190	2,273	48.2	5.08	836	11,091	
			9-19-49		1,079	3,352	53.0	4.58	4,715	15,806	
			11-28-49	N.P.	212	3,564	17.7	4.08	276	16,082	
78	247	Graves	1-25-49	30	509	509	59.0	5.0	917	917	318
			1-28-49	30	3,177	3,686	66.5	5.1	6,465	7,382	
			3-21-49		304	3,990	6.4	± 1.0	11	7,394	
			11-10-49	-10	164	4,154					
80	252	Graves	2-1-49		453	453	42.9	4.75	819	819	206
			2-7-49	20	3,743	4,196	58.1	5.5	10,764	11,584	
			3-23-49		274	4,470	47.0	7.05	1,090	12,675	
			4-5-49	15	1,119	5,589	63.6	4.75	4,055	16,730	
			5-31-49		252	5,841	57.6	4.08	710	17,440	
			8-22-49		212	6,053	54.7	5.58	778	18,218	
			8-30-49		2,521	8,574	57.3	6.0	10,400		
			9-30-49		177	8,751				19,074	
			10-25-49	N.P.	209	8,960	43.4	5.25	855	19,927	
			11-15-49	N.P.	196	9,156	48.5	5.0	853		
			2-6-50		168	9,324					
			81	263	Graves	2-23-49	50	470	470	65.7	
3-28-49	60	280				750	84.6	4.42	314	615	
4-1-49	60	6,477				7,227	78.8	5.54	8,428	9,043	
5-16-49	15-20	333				7,560	78.6	5.83	1,568	10,611	
6-1-49		472				8,032	65.5	4.25	1,345	11,957	
8-8-49	10	179				8,211	58.7	7.0	1,320	13,278	
8-17-49		594				8,805	65.0	6.33	4,399	17,678	
10-10-49	N.P.	188				8,993	58.9	4.42	881	18,559	
10-18-49		1,038				10,031	28.5	3.92	2,086	20,646	
83	271	Normal	3-14-49	N.P.	288	288	22.2	5.17	595	595	212

Table 9. (Cont.)

Patient		Diagnosis	Date of each treat.	Gland wt.	¹³¹ I, μ c	Cumulative	Max. uptake	Effect. half-life	Indiv. dose in rep. in thyroid	Cumulative dose in rep. in thyroid	Duration of hematol. obs., days
Hemat. lab.	¹³¹ I lab.										
84	284	Graves	4-6-49	60	286	286	80.7	4.75	3,923	3,923	
			4-14-49		5,200	5,486	80.0	6.2	9,285	13,208	
			6-1-49	50	517	6,003	75.1	4.25	629	13,838	
			6-8-49		5,787	11,790	78.5	4.2	6,873	20,712	
			8-3-49		282	12,072	68.6	2.7	189	20,901	
			8-11-49	50	11,367	23,439	71.2	3.16	9,217	30,118	
85	6	Carcinoma	1-6-46		940	940					
			3-7-49		1,918	2,858					
			4-27-49		3,675	6,533	10.1				
			5-10-49		9,092	15,625	9.0				
			6-16-49		159,972	175,597					
86	294	Graves	5-4-49	120	940	940	65.9	4.25	473	473	
			5-10-49		13,254	14,194	69.3	6.66	11,021	11,495	
			8-8-49		421	14,615	41.0	5.23	325	11,820	
			8-18-49	50	6,881	21,496	53.3	4.17	5,505	17,326	
			10-4-49	30	169	21,665	25.4	3.83	98	17,425	
			11-28-49	20	188	21,853	39.3	2.83	188	17,613	
			1-31-50	20	163	22,016					
88	323	Graves	9-20-49		293	293	66.1	4.5	224	224	
			9-28-49	70	14,235	14,528	62.6	2.54	5,820	6,044	
			10-13-49		173	14,701					
			10-19-49	35	171	14,872					
			10-26-49	35	211	15,083					
89	42	Carcinoma	11-15-46		489	489					
			12-6-46		3,760	4,249					
			12-27-49		923	5,172					
			1-25-50		999	6,171					
			1-28-50		50,700	56,871	65.0 per cent excretion from urine in 48 hours				
			2-28-50		1,220	58,091	74.0 per cent excretion from urine in 48 hours				
			3-3-50		97,909	156,000					

Platelets. Irregular transient reductions to as low as 130,000/cu mm from a general average level of approximately 220,000/cu mm have been observed, but they appear to be totally unrelated to the administration of radioiodine.

Case No. Hemat-56 Iod-105

Hemoglobin and Erythrocytes. The erythrocyte count remained unchanged at a general average level of approximately 5,400,000/cu mm, but the hemoglobin dropped from 17.8 to 15.8 g during the period of observation.

Leukocytes. The leukocyte count and the differential count showed no significant change during the period of observation.

Platelets. The platelets decreased in number from 170,000 to 120,000/cu mm at the end of the observation period. This is probably not a significant change.

Case No. Hemat-62 Iod-125

Hemoglobin and Erythrocytes. There was a gradual rise from 4,340,000 erythrocytes per cubic millimeter and 10.9 g hemoglobin on Oct. 29, 1947, to 5,330,000 erythrocytes and 14.9 g hemoglobin on Apr. 27, 1948. Approximately the same values were maintained during the remainder of the period of observation. These changes are most likely due to factors other than the administration of radioiodine.

Leukocytes. The total leukocyte count showed no significant change during the period of observation.

The absolute number of neutrophils fluctuated irregularly between 2120 and 6930/cu mm, and the relative percentage fluctuated between 42 and 76 per cent during the first 308 days of observation. For the remainder of the period they varied in absolute numbers between 1480 and 3040/cu mm and in percentage between 30 and 45 per cent. During the latter period, on one occasion one myelocyte and one metamyelocyte per 300 cells were observed, and on another occasion one metamyelocyte per 300 cells was observed. Throughout the period of observation the number of lymphocytes had a roughly inverse relation to the number of neutrophils. It should be noted that the first 308 days fell within the period of employment of one technician and the remainder of the period during the employment of her successor. The absolute number of eosinophils was approximately 110/cu mm during the first 28 days of observation and then rose sharply to a level of approximately 250/cu mm thereafter. None of the changes in the differential white blood cell count appeared to be related to the administration of radioiodine.

Platelets. There was a sharp decrease from a range of 250,000 to 320,000/cu mm to a range of 190,000 to 240,000/cu mm associated with the change in technicians between observations recorded on the dates of June 22, 1949, and Sept. 15, 1949.

Case No. Hemat-63 Iod-116

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-64 Iod-157

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-65 Iod-158

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-66 Iod-138

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-67 Iod-162

Hemoglobin and Erythrocytes. There was a gradual fall in the hemoglobin values from 12.3 to 8.6 g and in the erythrocyte count from 4,510,000 to 3,020,000/cu mm probably associated with the progress of the underlying disease. The patient expired shortly after the last recorded observation.

The leukocyte count, differential count, and platelet count showed no significant change during the period of observation.

Case No. Hemat-69 Iod-179

The complete hematological data on this patient showed no significant change during the period of observation.

Case No. Hemat-71 Iod-207

This case was complicated by the administration of external radiation. No significant changes in the hematological data due to radioiodine were observed.

Case No. Hemat-72 Iod-208

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-73 Iod-206

Hemoglobin and Erythrocytes. The hemoglobin and erythrocytes showed no significant change attributable to radioiodine.

Leukocytes. There was a persistent slight leukocytosis in the region of 14,000 to 16,000/cu mm for six months after the administration of 2072 μ c of radioiodine. It is not likely that this change has any relation to radioiodine. The differential and platelet counts showed no significant change during the period of observation.

Case No. Hemat-74 Iod-209

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-75 Iod-232

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-76 Iod-240

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-78 Iod-247

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-80 Iod-252

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-81 Iod-263

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-83 Iod-271

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-84 Iod-284

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-85 Iod-6

Hemoglobin and Erythrocytes. There was a gradual decrease in hemoglobin values from 14.2 to 12.6 g and in the erythrocyte count from 5,510,000 to 4,510,000/cu mm. The patient expired from underlying disease shortly after the last recorded observation.

Leukocytes. The total leukocyte count showed a preterminal elevation of the leukocytes to 12,500/cu mm.

There was a preterminal elevation of the neutrophils to 85 per cent.

Platelets. The platelet count showed no significant change.

Case No. Hemat-86 Iod-294

The complete hematological data on this case showed no significant change during the period of observation.

Case No. Hemat-88 Iod-323

The hemoglobin values, erythrocyte count, leukocyte count, and the platelet count showed no significant change during the period of observation.

There was insufficient data for analysis of the differential count.

Case No. Hemat-89 Iod-42

The complete hematological data showed no significant change during the period of observation.

Summary

1. No significant change in hemoglobin concentration, erythrocyte count, total leukocyte count, differential leukocyte count, or platelet count was observed in 17 of the 25 cases analyzed.

2. The hematological changes which were observed in eight patients showed no constant trend and could have been due to factors other than the administration of radioiodine.

DOSE-EFFECT RELATION—COMPARISON OF X-RAY, P³², AND I¹³¹ EFFECTS

Total-body X-ray Exposure

Hematological changes observed following total-body exposure to ionizing radiation show little relation between the type and quality of the radiation source and the change produced. This suggests the actual common denominator underlying all hematological changes is the total energy accrued by the tissues. The conventional units, r, rep, e.r., refer indirectly to energy absorbed in a unit mass of tissue. Usually radiation doses are expressed in terms of the central beam skin dose or central beam tissue dose calculated at an arbitrary depth. In total-body exposure either expression is ambiguous because (1) the total energy accrued by the tissues from a given skin dose varies with the quality of radiation; and (2) the total energy accrued by all tissues depends on (a) total mass of tissues, (b) spatial relation of the radiating source and the irradiated body, (c) depth at which the radiation dose is calculated, and (d) quality of radiation.

When effects following external irradiation are compared with those observed after internal irradiation as with radioisotopes these problems are complicated further.

In previous reports reference has been made to the difficulties of comparing effects following X rays, radiophosphorus, and radioiodine. During the current reporting period attention has been directed to the calculation of an "integral dose" which should more truly reflect the total energy accrued by the tissues. The method of calculation which was employed in these studies was developed by W. L. Mayneord¹ and is based on experimental determination of integral dose in a facsimile of a human body of average bodily dimensions consisting of material of uniform density. Despite obvious weaknesses, it is nevertheless the best approach for calculation of energy absorbed in tissues. Mayneord's method of calculating integral dose from external radiation is based on body weight, anteroposterior thickness of the trunk, half-value layer of radiation, linear absorption coefficient for the particular radiation, and the target-skin distance.

For the three qualities of X rays employed in these studies, namely, 100 kv, with a half-value layer of 1.35 mm aluminum, 200 kv with a half-value layer of 0.72 mm copper, and 1000 kv with a half-value layer of 9 mm copper for an average patient of 60 kg weight with a mean anteroposterior body thickness of 20 cm and a target-skin distance (T.S.D.) of 230 cm, the integral dose in megagram-roentgens relative to a central beam skin dose according to Mayneord's calculation is as follows:

$$\begin{aligned}\Sigma D \text{ for HVL} = 1.3 \text{ mm Al} &= 0.0144 D_0 \text{ megagram-r} \\ \Sigma D \text{ for HVL} = 0.72 \text{ mm Cu} &= 0.0343 D_0 \text{ megagram-r} \\ \Sigma D \text{ for HVL} = 9.0 \text{ mm Cu} &= 0.0416 D_0 \text{ megagram-r}\end{aligned}$$

where ΣD = integral dose and D_0 = skin dose.

These calculations show that in order to deliver the same integral dose the skin dose with 100 kv must be approximately twice that for 200 kv and approximately three times that for 1000 kv.

For example, to deliver an integral dose of 12 megagram-r, the following skin doses are necessary:

100 kv	830 r
200 kv	350 r
1000 kv	290 r

Similarly, for a given skin dose, e.g. 300 r, the integral doses will be

100 kv	$\Sigma D = 4.3$ megagram-r
200 kv	$\Sigma D = 10.2$ megagram-r
1000 kv	$\Sigma D = 12.6$ megagram-r

Table 7 shows the physical factors, skin dose, 10 cm depth dose, and the integral dose for the 32 patients who received total-body X-ray treatment.

According to calculations used herein, six patients received doses of 10 megagram r-with 200-kv generated X rays (3, 8, 9, 10, 11, 12). Analysis of blood counts on these patients during the period covering treatment and 100 days from the beginning of treatment shows the following:

Erythrocyte Count. Two patients showed significant decrease, three patients showed no change, data are lacking for one patient.

Platelets. Three patients showed significant decrease, data are lacking for three patients.

Leukocyte Count. Five patients showed significant increase, one patient showed significant decrease, one patient showed both an increase and a decrease.

Lymphocytes. Four patients showed significant increase, two patients showed significant decrease only, and two patients showed a significant decrease as well as a significant increase.

Monocytes. Six patients showed significant increase. In five of the patients the increase is very marked.

Table 7—Total-body Irradiation: Patients Treated with X Rays (1-32)*

No.	Kv	No. of expos.	Duration of Rx, days	Skin dose, r per day	Total skin dose, r	10 cm. depth dose, r	Integral dose in megagram-r	Duration of obs., days
1	200	22	27	15	321	207	11.0	480
2	200	8	58	50	394	264	13.5	130
3	200	21	24	10 or 20	295	198	10.1	150
4	100	3		30	72		1.0	
	200	9		30	295		10.1	
		<u>12</u>	89		367	246	11.1	730
5	100	10		10	104		1.5	
	200	18		10	187		6.4	
		<u>28</u>	59		291	125	7.9	840
6	200	20	25	10 or 20	244	164	8.4	36
7	100	3		20	60		.9	
	200	23		10	235		8.1	
		<u>26</u>	30		295	140	9.0	36
8	200	19	22	15	302	202	10.4	74
9	200	14	16	20	300	201	10.3	2309
10	200	15	17	20	307	206	10.5	2337
11	200	15	17	20	300	201	10.3	2436
12	200	15	17	20	313	210	10.7	46
13	200	13	15	20	258	173	8.9	780
14	1000	5	5	20	100	68	4.2	79
15	1000	5	6	20	100	68	4.2	88
16	1000	5	6	20	100	68	4.2	620
17	1000	6	7	20	120	82	5.0	37
18	1000	5	5	20	100	68	4.2	660
19	1000	14	17	20	283	192	11.8	1438
20	1000	15	17	20	300	204	12.5	21
21	1000	21	20	20	292	199	12.1	1210
22	1000	15	18	20	300	204	12.5	1746
23	1000	15	19	20	302	205	12.6	420
24	1000	6	7	20	120	82	5.0	1253
25	1000	2	2	20	40	27	1.7	2
26	1000	26		10	259		10.8	
	200	4		10	40		1.4	
		<u>30</u>	38		299	203	12.2	350

Table 7—(Continued)

No.	Kv	No. of expos.	Duration of Rx, days	Skin dose, r per day	Total skin dose, r	10 cm depth dose, r	Integral dose in megagram-r	Duration of obs., days
27	1000	27		10	271		11.3	
	200	3		10	30		1.0	
		30	40		301	204	12.3	585
28	1000	17		5	85		3.5	
	200	41		5	213		7.3	
		58	92		298	201	10.8	1120
29	1000	15		5	75		3.1	
	200	37		5	203		7.0	
		52	68		278	187	10.1	351
30	100	30	36	10	298		4.3	1232
31	100	30	36	10	299		4.3	1234
32	100	14	19		303		4.4	32

*Total integral dose for 60-kg patient, F.S.D. = 230 cm; mean anteroposterior thickness = 20 cm; average dimensions:

100 kv: $\Sigma D = 0.0144 D_0$ megagram-roentgen HVL = 1.35 mm Al
 200 kv: $\Sigma D = 0.0343 D_0$ megagram-roentgen HVL = 0.72 mm Cu
 1000 kv: $\Sigma D = 0.0416 D_0$ megagram-roentgen HVL = 9.0 mm Cu

Three patients received doses of 12 megagram-roentgens with 1000-kv generated X rays (21, 22, 23). Hematological changes during approximately 100 days following beginning of treatment are as follows:

Erythrocyte Count. Three patients showed significant decrease.

Platelets. Three patients showed significant decrease.

Leukocytes. Two patients showed significant increase during the first five days. One patient showed no change during this period. Three patients showed significant decrease between the 20th and 60th days.

Lymphocytes. Two patients showed significant decrease during the first 20 days. One patient showed no change during this period. Three patients showed significant decrease between the 20th and 130th days.

Monocytes. Three patients showed significant increase during the first 30 days.

Three patients received 4 megagram-roentgens with 1000-kv generated X rays (14, 15, 16). Hematological changes during the 100 days following beginning of treatment are as follows:

Erythrocyte Count. Two patients showed significant decrease. One patient showed significant increase.

Platelets. Two patients showed no change. Data are lacking on one patient.

Leukocytes. Two patients showed significant decrease; one patient showed significant increase.

Lymphocytes. Two patients showed significant increase; one patient showed significant decrease.

Monocytes. Three patients showed significant increase. Two of these patients showed significant decrease followed by significant increase.

Three patients received 4 megagram-roentgens with 100-kv generated X rays (30, 31, 32).

Hematological changes observed during the first 60 days after beginning of treatment are as follows:

Erythrocyte Count. Two patients showed significant decrease. One patient showed no change.

Platelets. Three patients showed no change.

Leukocytes. Two patients showed significant decrease. One patient showed no change.

Lymphocytes. One patient showed a significant decrease only. Two patients showed both significant increase and significant decrease.

Monocytes. Three patients showed no change.

For the first group of patients, those who received 10 megagram-roentgens with 200 kv, the behavior of the monocytes is entirely consistent. The leukocyte count is almost entirely consistent. The lymphocyte count is fairly consistent. Data are not sufficient to evaluate the consistency of platelet counts. The erythrocyte count is not consistent.

The second group of patients, those who received 12 megagram-roentgens with 1000 kv showed complete consistency of erythrocyte count, platelets, leukocytes, lymphocytes, and monocytes.

The third group of patients, those who received 4 megagram-roentgens with 1000 kv, showed complete consistency only with respect to monocytes. Behavior of platelets is the same in two patients, i.e., unchanged, and for the third patient data are lacking. Erythrocyte, leukocyte, and lymphocyte counts show no consistency.

The fourth group of patients, those who received 4 megagram-roentgens with 100 kv, show consistency of monocytes and platelets, both of which remain unchanged in the three patients. Erythrocytes, leukocytes, and lymphocytes show no consistency. These observations show (a) that integral doses in excess of 10 megagram-roentgens have a depressing effect, which may be transitory, on all blood elements and (b) that integral doses around 4 megagram-roentgens may produce varying transitory effects upon the different blood elements apparently dependent upon the lability of each of these elements, without uniform trend of the reactions (see Fig. 4).

Radiophosphorus

When P^{32} is given internally in the form of Na_2HPO_4 as a source of radiation, energy accrued by the tissues can be calculated if the amount of P^{32} retained by the body, the rate of excretion, and the distribution of P^{32} in the body are known.^{2,3} Rate of excretion and its reciprocal, the amount retained in the body, have been determined for a large number of individuals in previous studies.⁴ The results have been confirmed in some of the patients included in the present study. Distribution of P^{32} in the body at any given time is almost impossible to determine because of constant metabolic flux. One may assume uniform distribution, or more accurately, it may be supposed that after an initial equilibration period the P^{32} is distributed in two main compartments, namely, soft tissue and bone. It may be mentioned that bone is known to have the greatest avidity for phosphorus of any tissue in the body, including tumor tissue.

For the purpose of developing a basis for calculation it is assumed that the initial distribution of P^{32} is uniform throughout the body. After 3 days specific concentration in bone is presumed to be 10 times greater than in soft tissue. Two criticisms of these assumptions can be made. First, the ratio 10/1 for bone and soft tissue expresses the highest possible ratio rather than an average; second, the ratio for bone and soft tissue is established gradually over a period of time and not at the end of 3 days. One should be guided by these assumptions, nevertheless, for the sake of the patient's safety. By assuming the highest possible concentration of P^{32} in bone in each case, one is deterred from administering doses which might produce hematological damage. By assuming abrupt establishment of the bone-soft tissue ratio of P^{32} concentration, the calculation of dosage is facilitated through the elimination of complex mathematical procedures.⁵

Table 8 shows the treatment data and the calculated dose distribution in the two compartments, as well as the whole-body integral dose.

The integral dose received by these patients varied from 3.72 to 4.97 megagram-roentgens. Calculation of dose on the basis of two-compartment distribution shows that the bone dose varied from 253 to 374 rep (gram-r/gram) while the soft tissue dose varied from 29 to 47 rep (gram-r/gram).

The trend of hematological changes observed in these patients during the first 100 days after beginning of treatment was in general similar. Marked individual variations were observed, however, and changes occurred at different times and showed marked differences of degree.

The most striking changes were observed in these patients in platelet and leukocyte counts, which could be explained by the high bone dose as compared with the soft tissue dose.

Table 8— Total-body Irradiation: Patients Treated with P³² (Na₂HPO₄ Intravenously) (33-54)

Pt. no.	No. of adm.	Dura. of Rx	Total mc	Fractionation								Wt, kg	Two compart. dose in rep*		Total integral dose, megagram-r	Dura. of obs., days	
				mc	Days	mc	Days	mc	Days	mc	Days		Soft tissue	Bone			
33	5	28	8.00	2	7	2	7	2	7	1	7	1	67	42.1	365	4.97	672
34	4	21	6.38	2	7	2	7	.76	7	1.62			56	40.0	347	3.96	833
35	4	21	8.00	2	7	2	7	1	7	3			67	42.1	365	4.97	1108
36	4	20	6.70	2	6	2	7	2	7	.7			58	40.0	353	4.16	1020
37	4	21	6.48	2	7	1.55	7	2.45	7	.48						4.03	211
38	4	21	6.66	2	7	2	7	2	7	.66			68	34.3	298	4.14	446
39	4	41	8.00	2	7	2	7	2	27	2			65	43.1	374	4.97	874
40	3	14	6.00	2	7	2	7	2					65	32.3	280	3.72	78
41	3	39	6.00	2	32	2	7	2					44	47.7	415	3.72	1126
42	4	40	6.82	2	26	2	7	2	7	.82			79	30.2	263	4.23	1120
43	2	7	3.65	2	7	1.65	Patient did not return						63	20.3	177	2.27	7
44	4	21	8.02	2.01	7	2	7	2	7	3.01			86	32.8	285	4.98	115
45	4	20	8.00	2	7	2	7	2	6	2			65	43.1	374	4.97	852
46	4	20	8.02	2.02	7	2	6	2	7	2			73	38.4	334	4.98	1008
47	4	22	8.00	2	8	2	7	2	7	2			88	31.8	276	4.97	808
48	4	23	8.03	2	7	2	7	2.03	9	2			65	43.2	376	4.99	119
49	4	21	8.00	2	7	2	5	2	9	2			89	31.8	276	4.97	454
50	4	21	8.00	2	7	2	7	2	7	2			73	38.4	333	4.97	602
51	4	21	8.00	2	7	2	7	2	7	2			77	36.5	317	4.97	137
52	4	21	8.00	2	7	2	9	2	7	2			71	39.8	346	4.97	634
53	3	14	6.00	2	7	2	7	2					72	29.2	253	3.72	662
54	3	14	6.00	2	7	2	7	2					64	32.9	286	3.72	631

*1r = 1 gram-r/gram; 1 megagram-r = 10⁶ gram-r.

The general inconsistency of hematological changes is comparable to observations on the X-ray-treated patients who received low integral doses, similar in magnitude to the integral doses administered to the patients treated with P^{32} .

A mathematical correlation between energy accrued and biological effect as shown by hematological changes has not been accomplished in these studies. The fact that some degree of correlation is indicated, however, suggests that by better control of experimental conditions a more exact relation between integral dose and hematological effect could be demonstrated. Such improvement of observational technique, together with a better understanding of the relation between bone and soft tissue dose resulting from use of internal sources of radiation, should make possible valid comparison between biological effects of X rays and radioisotopes (see Fig. 5).

Blood Clearance of Radioiodine and Dosage Calculation with I^{131}

From the hematological data it would appear at first sight that there is no relation between the amount of radioiodine administered and the occurrence of hematological changes. The changes observed following total-body X-ray irradiation and intravenous administration of P^{32} do strongly suggest a causal relation between the radiation received and the hematological effect. A plausible explanation of the absence of any characteristic hematological changes following administration of radioiodine may rest on several factors: (a) radioiodine is so definitely organ bound that only a small part of the dose administered actually exerts any total-body radiation effect, (b) the time during which any significant concentration of radioiodine is present throughout the body is very brief, and (c) concentration of radioiodine at the sites of hematopoiesis at any given time is apparently too low to produce hematological changes.

In order to investigate the role of these several factors more fully, blood clearance rates and rates of excretion of radioiodine have been studied for two of the patients (Hemat-55 and Hemat-89). Both patients had metastatic carcinoma of the thyroid and received totals of 468 mc of I^{131} and 156 mc of I^{131} , respectively.

Clearance rates were studied by the following method: Blood in amounts of 0.02 cc was drawn from the lobe of the ear into a blood-counting pipet at regular intervals following administration of radioiodine. Blood samples were taken until the radioactivity in the blood was too low to measure. The blood samples were pipetted onto a glass slide within a circle 1.2 cm in diameter previously drawn in the center of the slide with a wax pencil. The samples were dried in air. Radioactivity was determined with an end-window Geiger-Mueller counter with approximately 2 mg/cm² mica window, of a diameter 5.5 cm. A standard was prepared by mixing a known amount of radioiodine of the same specific activity as was administered to the patient with oxalated blood from a normal subject. After determination of radioactivity with the Geiger-Mueller counter, radioautographs were made of the samples. Exposure time was the same for all radioautographs.

Figure 6 shows radioautographs of the blood samples from patient Hemat-55 Iod-56, and indicates the amount of I^{131} administered, the quantities in the blood samples determined by assay.

These radioautographs illustrate the concentration curve of radioiodine in the blood as shown in Figs. 7 and 8.

Figures 9, 10, 11, 12, and 13 illustrate the blood concentration following the test and therapeutic doses of I^{131} in patient Hemat-89 Iod-42.

The same phenomenon as other investigators have reported, namely, a slight rise in concentration of radioiodine in the blood on the second day after administration of I^{131} , has been observed in most instances. This has been explained as due to release of organically bound radioiodine from the thyroid gland or from functioning thyroid tissue.

Excretion rates were studied by the following method: Urine was collected daily for 5 days immediately following administration of radioiodine. Aliquots were prepared, and the radioactivity was determined with a Geiger-Mueller counter. Figures 14 and 15 show urinary iodine excretion in patient Hemat-55 Iod-56.

Figure 16 shows blood clearance and urine concentration of I^{131} in patient Hemat-55 Iod-56. The initial very steep slope for both blood clearance and urine concentration extends over a period of 2 days, corresponding to a short biological half-life and is followed by a more gradual descending

slope corresponding to a longer biological half-life. The physical decay curve drawn into the figure is to contrast the biological and physical half-life.

From the data presented, the total circulating radioiodine can be calculated when the plasma volume is known. On the basis of established formulas,^{3,6,7} the gamma-ray and beta-ray dose can then be estimated (see Figs. 17, 18, and 19).

The dosage rate of beta radiation per millicurie per gram in rep per day is

$$d_{\beta} = 0.0125 \times 10^6 \times C \text{ rep/day}$$

where C is the concentration of I^{131} in the blood expressed in millicuries per gram.

The total integral beta-ray dose rate is

$$D_{\beta} = 0.0125 CW \text{ megagram-r/day}$$

where W is the weight of the patient in grams.

The value of C at any time can be determined from the blood-concentration chart either in millicuries or in per cent of administered dose.

The dose rate due to gamma radiation can be estimated on the basis of the following formula

$$d_{\gamma} = IAC_g$$

where IA is the intensity of γ radiation at 1 cm from a point source of 1 mc of I^{131} in rep per hour and g is a geometrical factor.

$$IA = 2.65 \text{ rep/hr/mc at 1 cm}$$

$$g = 200 \text{ for a cylinder (trunk) 60 cm long and 40 cm in diameter}$$

$$\therefore d_{\gamma} = 2.65 \times 200 \times C \text{ rep/hr at the center of the cylindrical body}$$

The calculation of integral dose from γ radiation becomes complex. An assumption has therefore been made that an average value of γ -radiation intensity for the whole body is half the intensity at the center. The true value may lie somewhere between these two.

$$\begin{aligned} \text{Av. } d_{\gamma} &= \frac{1}{2} \times 2.65 \times 200 \times 24 \times C \\ &= 0.0636 c \text{ megagram-r/day} \end{aligned}$$

and the combined integral dose rate is

$$\begin{aligned} \text{I.d.}(\beta + \gamma) &= (0.0125 + 0.0636) \times C \\ &= 0.0761C \text{ megagram-r/day} \end{aligned}$$

The maximum possible integral dose rate would be

$$\begin{aligned} \text{I.d.}_{\text{max}} &= (0.0125 + 0.1272) C \\ &= 0.1397C \text{ megagram-r/day} \end{aligned}$$

The estimated integral dose for each treatment for patient Hemat-89 Iod-42 is as follows:

	Administration		Internal dose	
	mc	Date	Amt.	Days
1	50.7	1-28-50	0.58	5
2	97.9	3-3-50	1.48	6
3	97.6	3-30-50	1.15	6
4	91.3	4-27-50	1.10	6
5	97.0	5-25-50	1.16	6

The small integral doses received by this patient explain the lack of significant hematological changes.

In summary, one may say that these calculations concerning integral dose and dose-effect relation are consistent with the observations made on patients treated with various qualities of X ray and radiophosphorus. The different blood elements of the bone marrow and peripheral blood respond to the equal amounts of ionizing radiations differently, depending upon the lability of each of these elements, when the energy accrued is below a certain integral value. When the dose exceeds that value which for X rays is around 10 megagram-roentgens, all blood elements respond similarly, namely, with a numerical depression of all cellular elements of the hemopoietic system.

SUMMARY

A total of 32 patients were treated with X rays generated by 100, 200, and 1000 kv. Individual exposures varied from 5 to 50 r measured on the body surface at each treatment. The total accumulated doses varied from 100 to 390 r total-body dose as measured on the skin. The calculated tissue dose in the central plane of the body varied from approximately 60 to 264 r. The total elapsed time from the first to the last treatment varied between 5 and 92 days. The 32 patients treated in this manner were followed hematologically for periods as long as possible after treatment. The longest period of observation for any member of the group is six and one-half years, the average for the group as a whole is approximately four years.

A total of 22 patients were treated with radiophosphorus for advanced generalized arthritis between September 1946 and May 1948. The longest observation period for this group is three years. These patients received individual doses at weekly intervals by the intravenous route, varying from 7000 μ c of P32 in the form of an aqueous solution of disodium hydrogen phosphate. The total dose varied from 3600 to 8000 μ c, and the treatment period varied from 7 to 21 days, with the exception of two patients who received their treatment in a period of 40 and 41 days, respectively.

The third group of patients, a total of 33, consisted of those who received radioiodine treatment for Graves' Disease and for thyroid malignancy. Carrier-free I¹³¹ in the form of sodium iodide was administered orally in amounts varying from a few hundred microcuries to 100,000 μ c in a single dose. Since May 1948, patients treated with radioiodine constitute the only new additions to our series.

REFERENCES

1. W. L. Mayneord, Energy Absorption. Part III. The Mathematical Theory of Integral Dose and its Applications in Practice, Brit. J. Radiology, XVII: 359 (1944).
2. L. D. Marinelli, Dosage Determinations with Radioactive Isotopes, Am. J. Roentgenol. Radium Therapy 47: 210 (1942).
3. L. D. Marinelli, E. H. Quimby, and J. G. Hine, Dosage Determination with Radioactive Isotopes. II. Practical Considerations in Therapy and Protection, Am. J. Roentgenol. Radium Therapy 59: 260 (1948).
4. B. V. A. Low-Beer, J. H. Lawrence, and R. S. Stone, Therapeutic Use of Artificially Produced Radioactive Substances: Radiophosphorus, Radiostrontium, Radioiodine, with special reference to Leukemia and allied Diseases, Radiology, 39: 573-597 (November 1942).

5. B. V. A. Low-Beer, R. S. Blais, and N. E. Scofield, Dosage Estimation for Intravenously Administered P^{32} , to be published in Am. J. Radiology.
6. W. E. Siri, Isotopic Tracers and Nuclear Radiations, pp. 414-431, McGraw Hill Book Company, Inc., New York, 1949.
7. B. V. A. Low-Beer, Clinical Use of Radio Isotopes, Charles C. Thomas, Springfield, 1940.

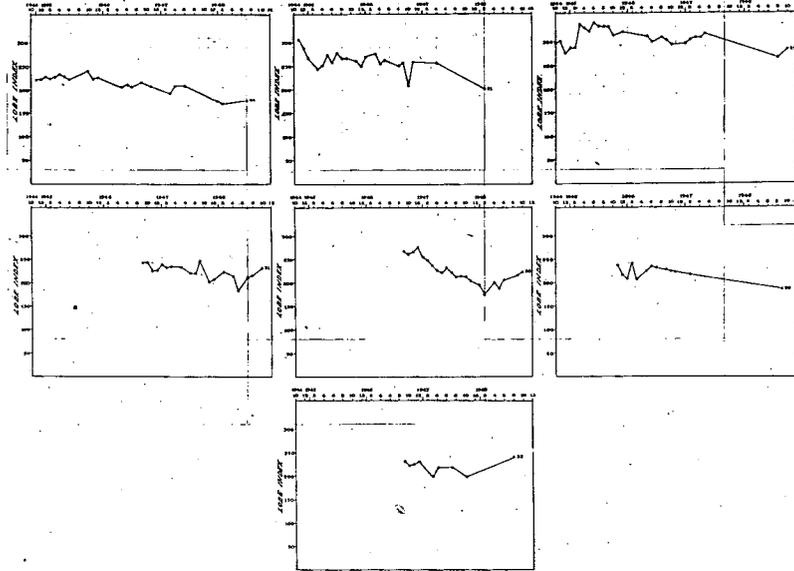


Fig. 1—Lobe index changes in seven patients analyzed individually.

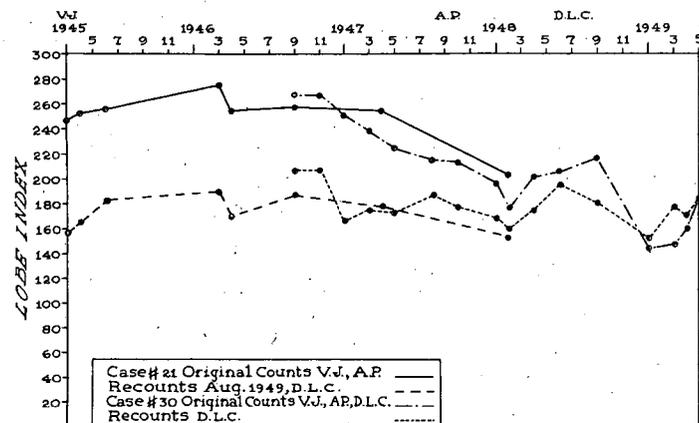


Fig. 2—Original values for the lobe index by the three technicians done between March 1945 and May 1949 compared with recounts on the same smears done by D.L.C. in August 1949 on cases 21 and 30. Note greater discrepancy in absolute figures at beginning, lesser discrepancy at end. While the trend of the original counts is downward, that of the recounts shows no such trend, although wide variations occur between individual counts.

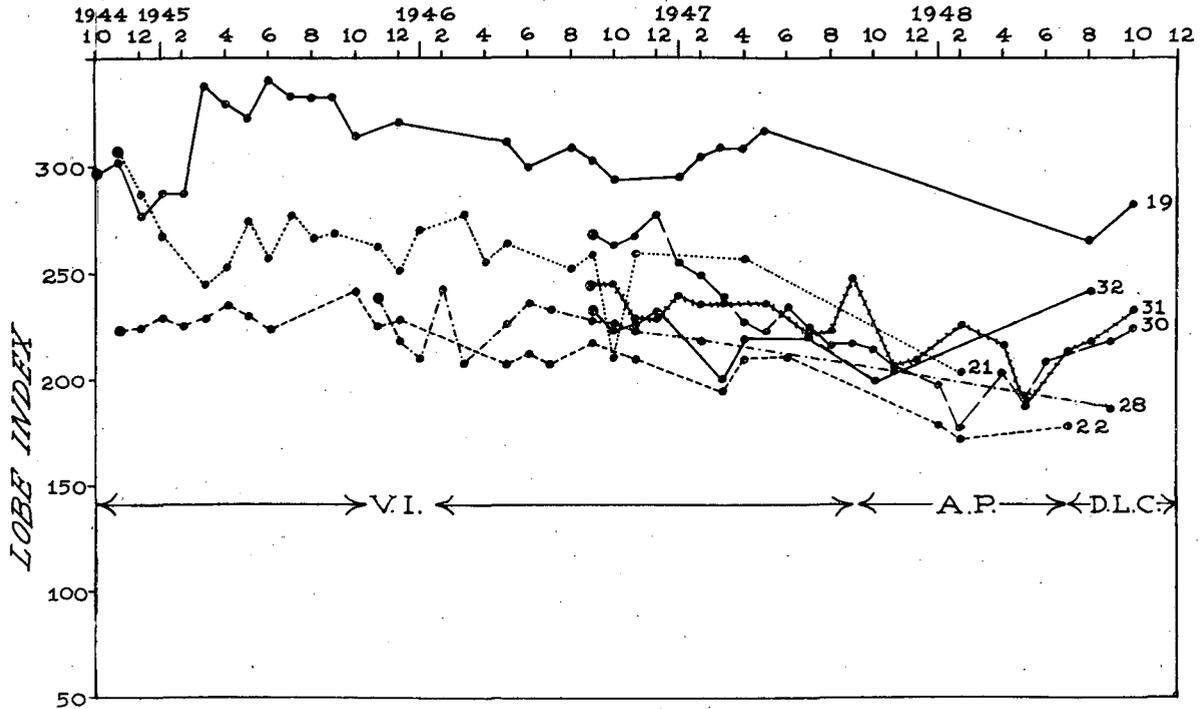


Fig. 3--Lobe index changes following total-body X-ray irradiation as reported by three subsequent technicians.

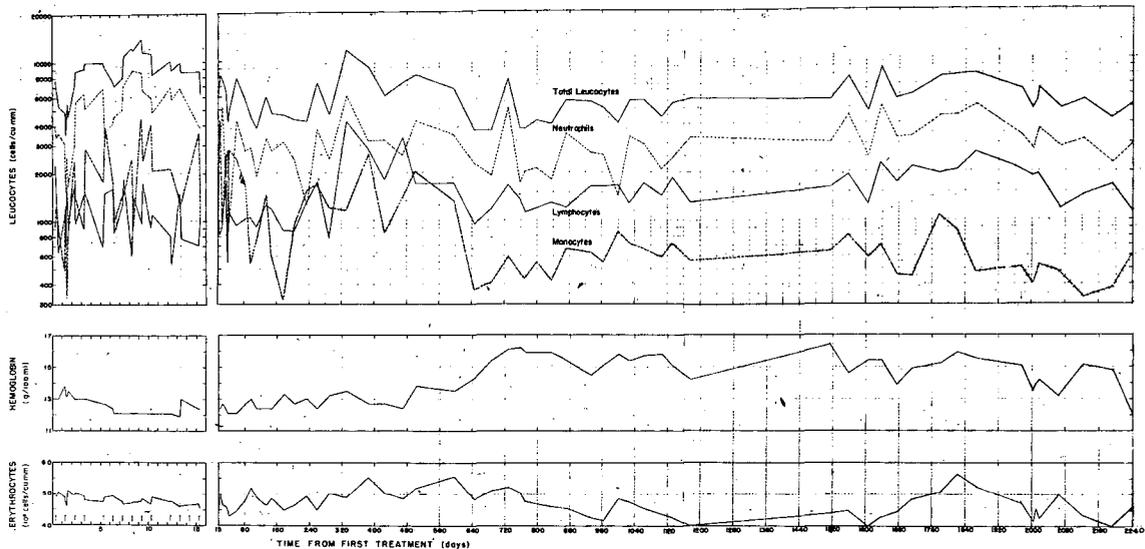


Fig. 4--Graph of a representative case (patient 9). Total-body X-ray treatment; technique 200 kv, HVL 0.95 mm Cu; 14 treatments in 16 days. Daily 20 r (skin). Total-body exposure 300 r (skin); whole-body calculated dose 201 r. Integral dose 10.3 megagram-roentgens.

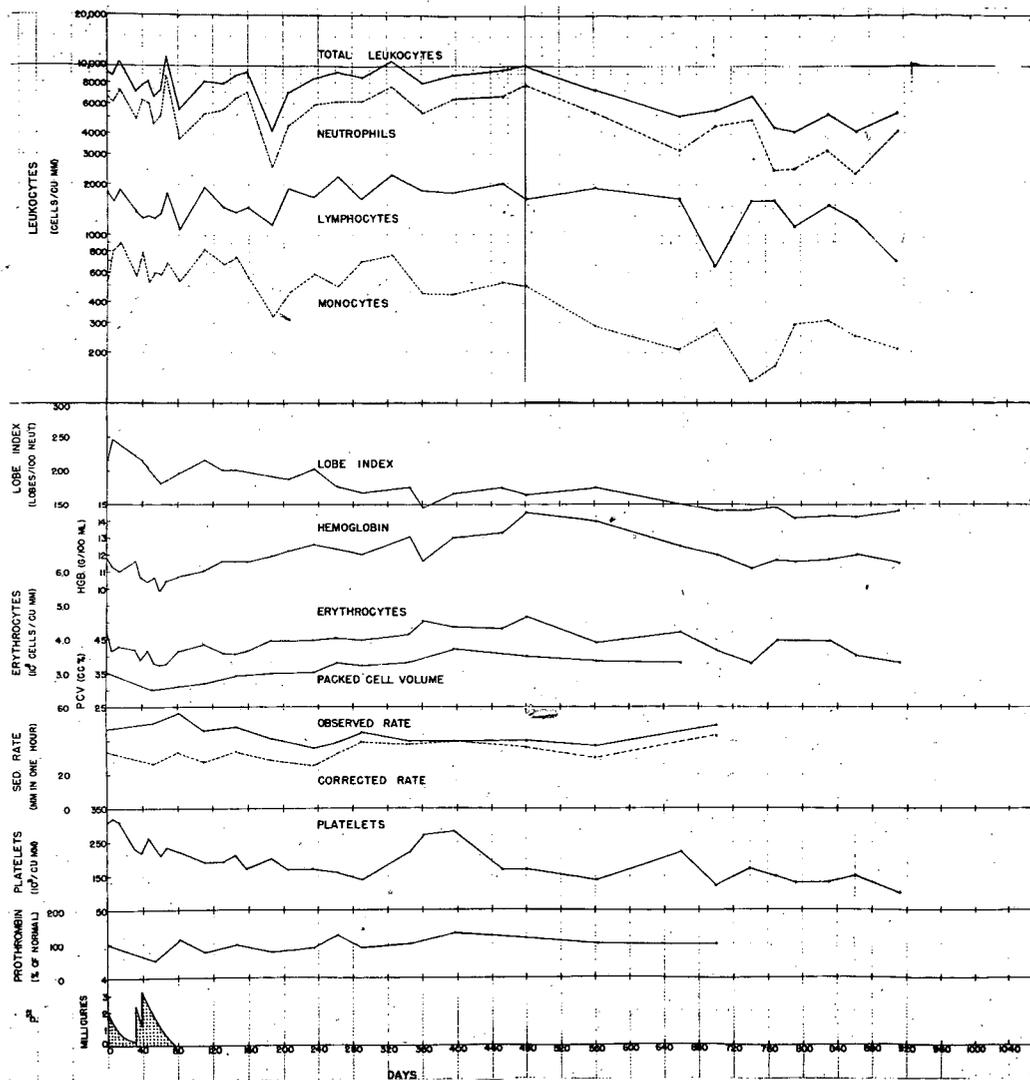


Fig. 5—Graph of a representative case treated with P^{32} (patient 41). Six millicuries of P^{32} in 40 days in three 2-mc doses of $Na_2HP^{32}O_4$ intravenously. Calculated total integral dose 3.72 megagram-roentgens. Estimated dose 47 rep, bone dose 415 rep.

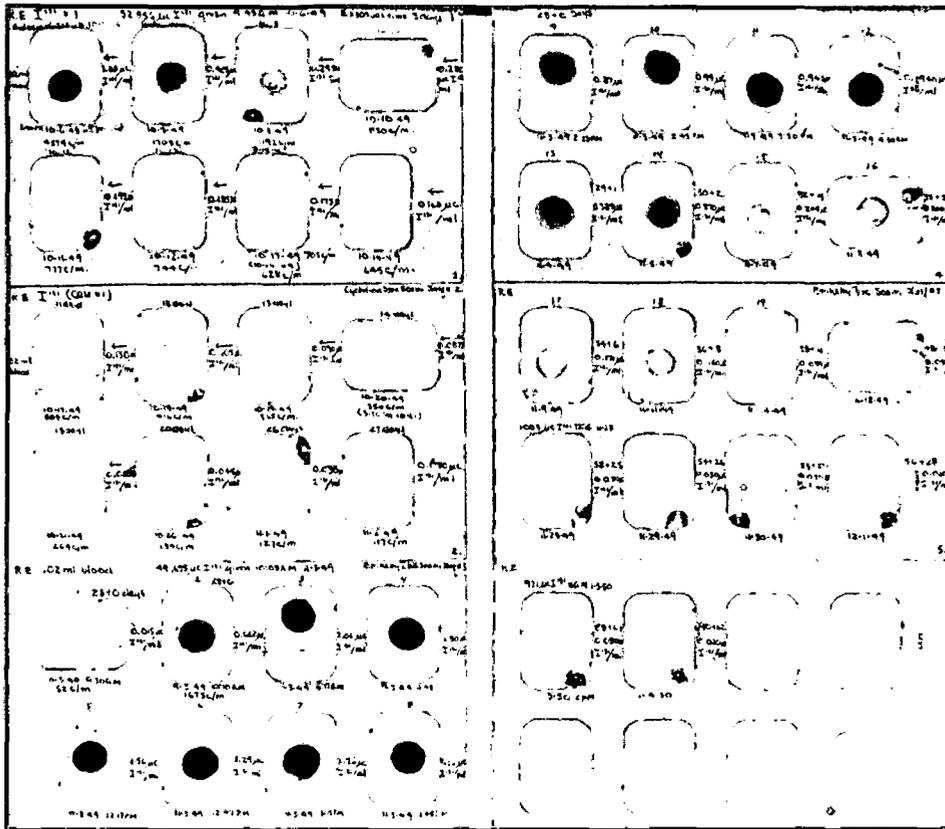


Fig. 6—Radioautographs of blood samples from patient Hemat-55. These indicate the amount of I^{131} administered and the quantities in the blood samples determined by assay.

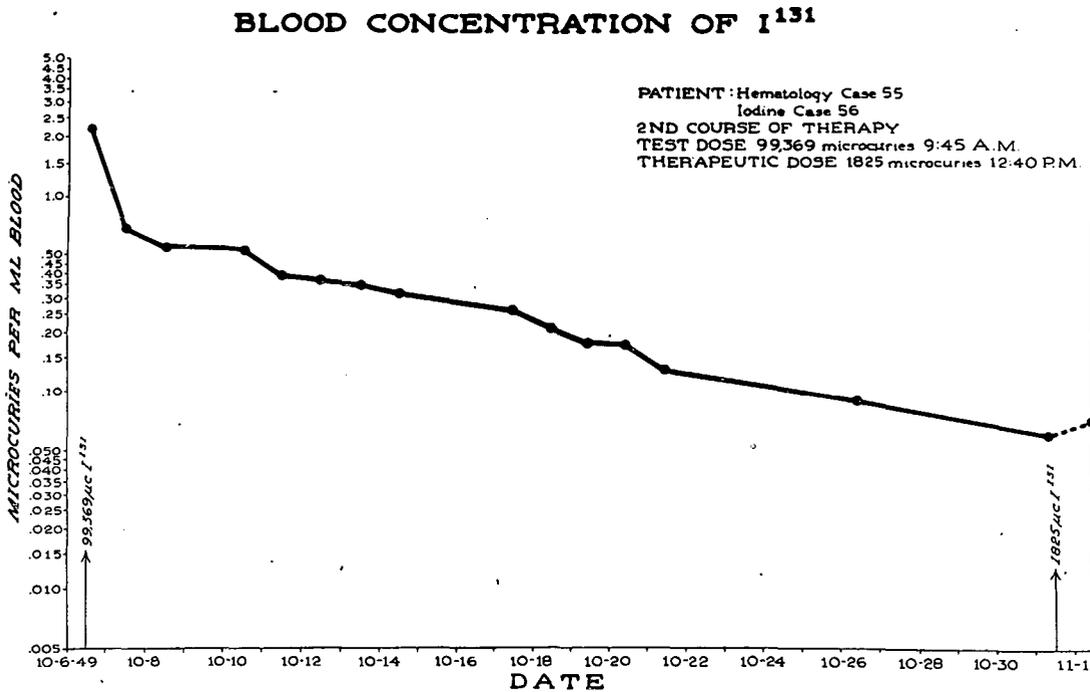


Fig. 7—Blood concentration of I^{131} after a therapeutic dose of approximately 99 mc of I^{131} administered orally.

BLOOD CONCENTRATION OF I¹³¹

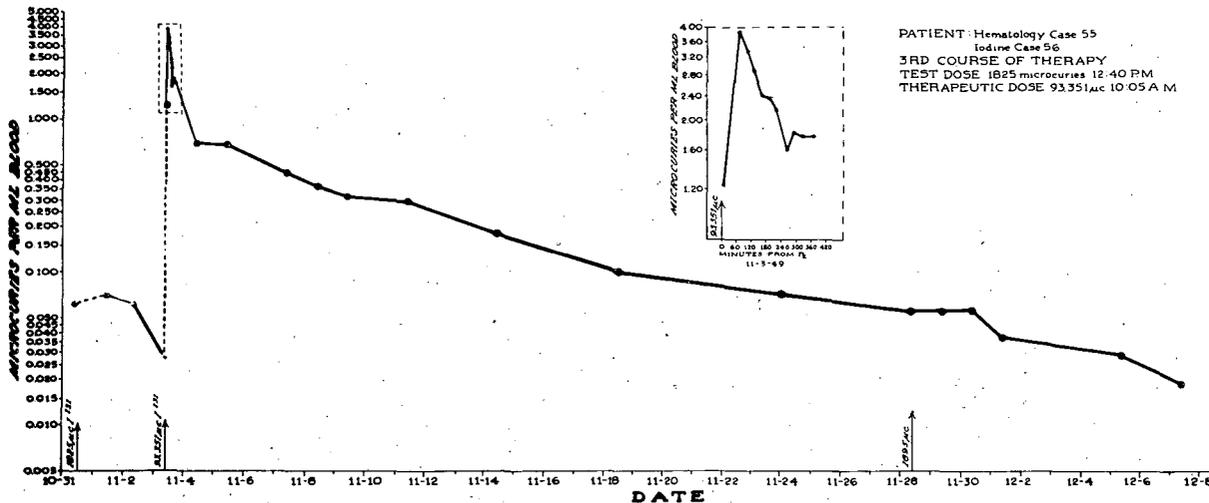


Fig. 8—Blood concentration of I¹³¹ following a test dose of 1.8 mc and a second therapeutic dose of approximately 93 mc of I¹³¹ and again followed by a test dose of 1.8 mc of I¹³¹ 26 days later. The inset shows blood concentration during the first 7 hr after administration of the therapeutic dose.

BLOOD CONCENTRATION OF I¹³¹

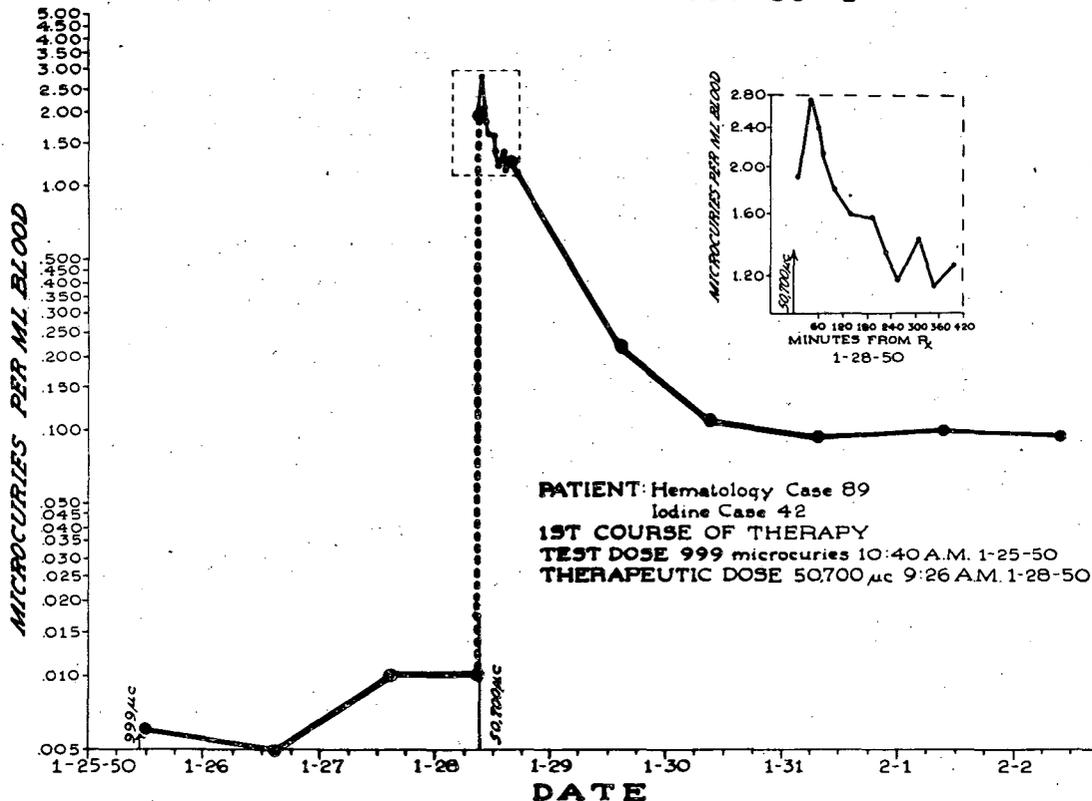


Fig. 9—Blood concentration curves of patient Hemat-89 Iod-42 following a test dose of 999 μ c and a therapeutic dose of 50,700 μ c of I¹³¹. The inset indicates the values in the first 7 hr.

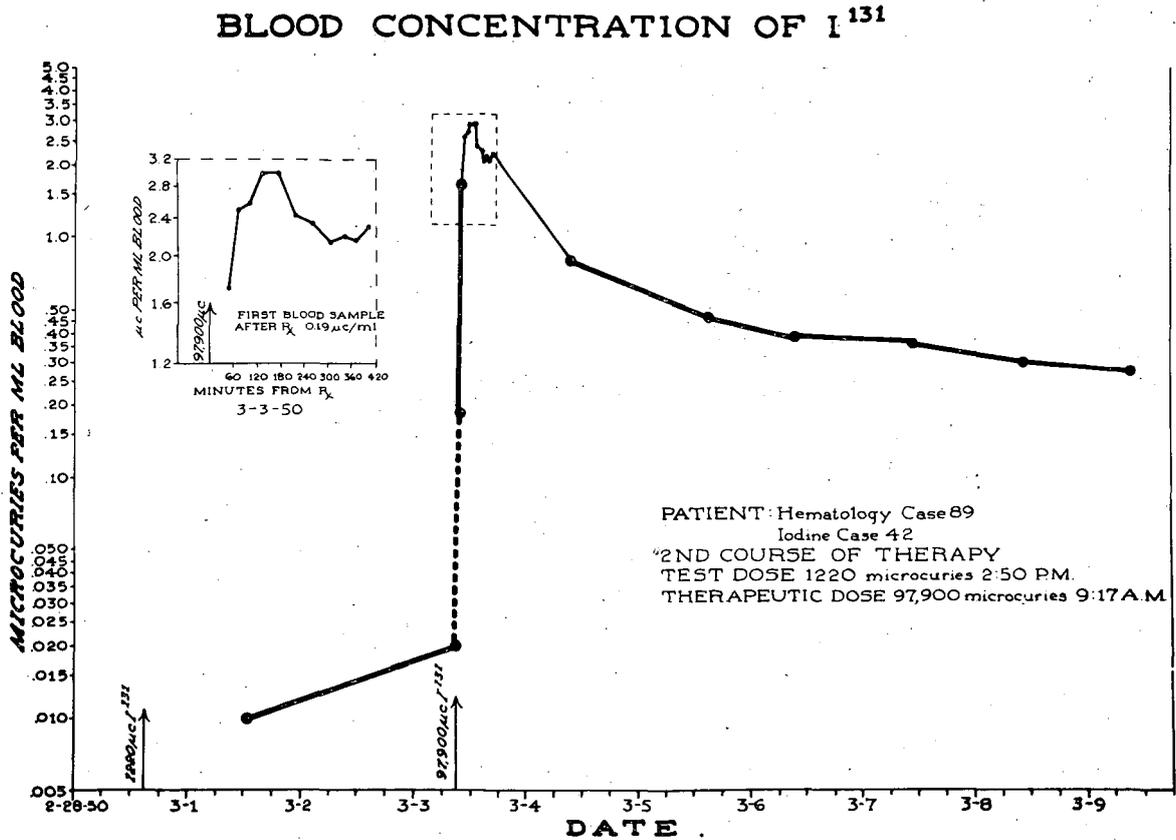


Fig. 10— Blood concentration curves of patient Hemat-89 Iod-42 following a test dose of 1220 μc and a therapeutic dose of 97,900 μc of I^{131} . The inset indicates the values in the first 7 hr.

BLOOD CONCENTRATION OF I¹³¹

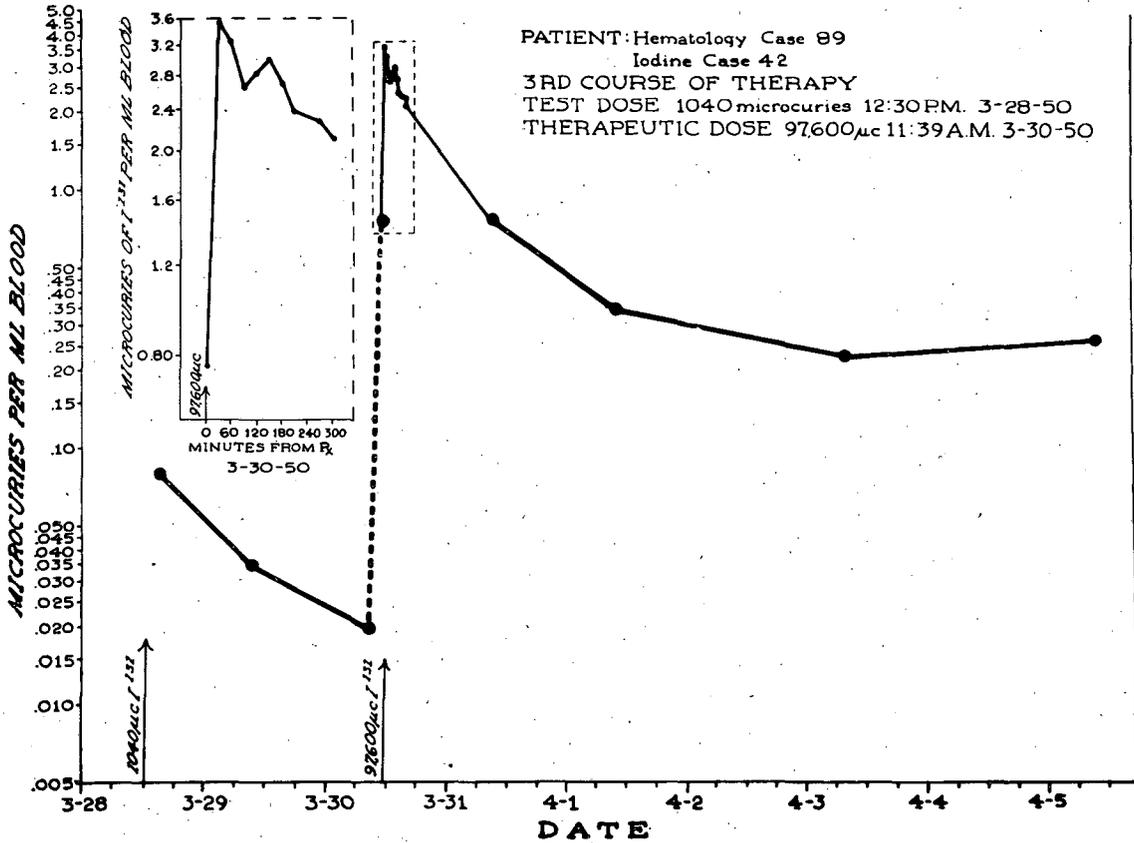


Fig. 11—Blood concentration curves of patient Hemat-89 Iod-42 following a test dose of 1040 μ c and a therapeutic dose of 97,600 μ c of I¹³¹. The inset indicates the values in the first 7 hr.

BLOOD CONCENTRATION OF I¹³¹

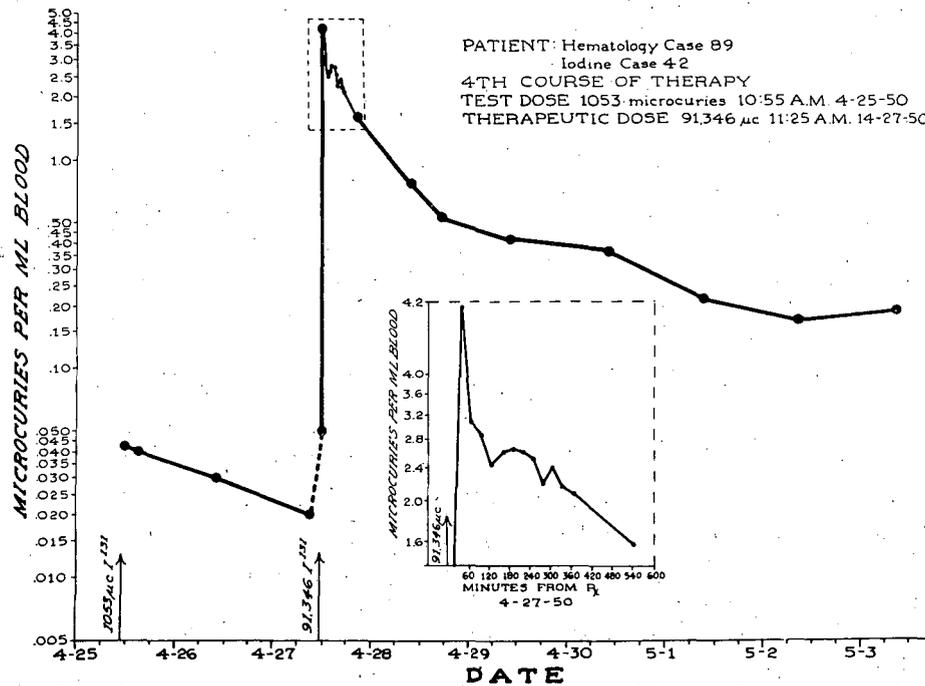


Fig. 12—Blood concentration curves of patient Hemat-89 Iod-42 following a test dose of 1053 μc and a therapeutic dose of 91,346 μc of I¹³¹. The inset indicates the values in the first 7 hr.

BLOOD CONCENTRATION OF I¹³¹

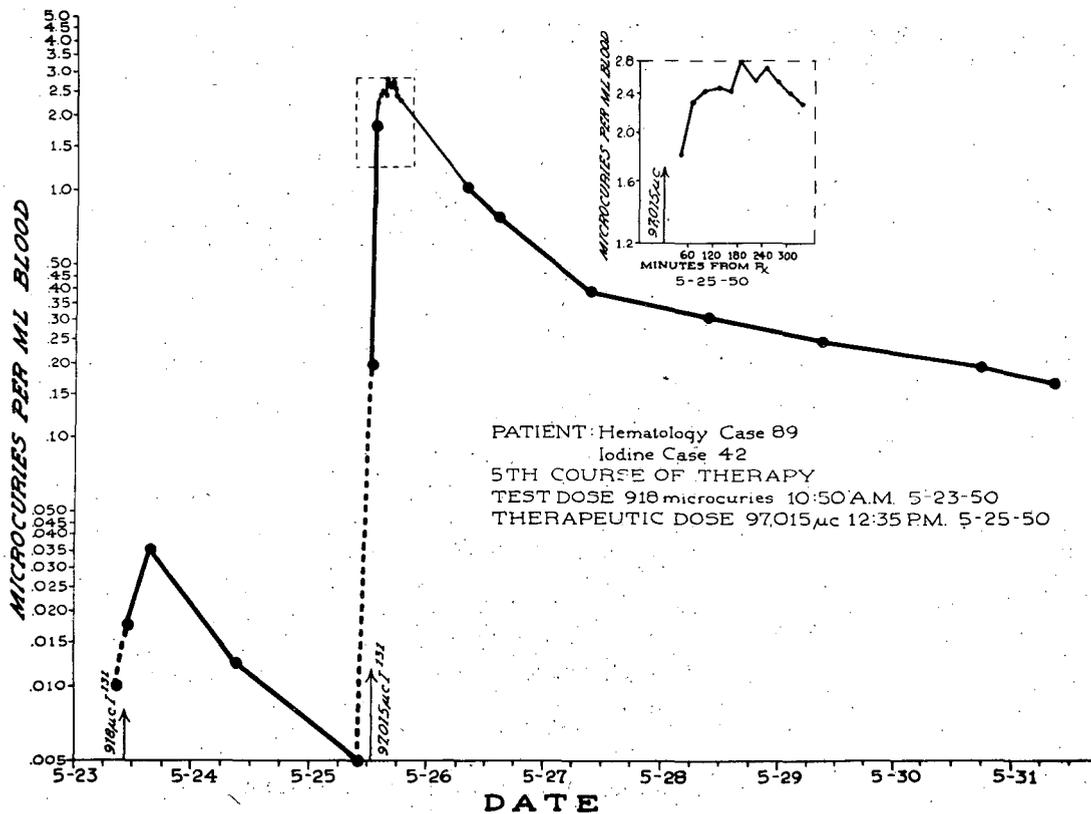


Fig. 13—Blood concentration curves of patient Hemat-89 Iod-42 following a test dose of 918 μc and a therapeutic dose of 97,015 μc of I¹³¹. The inset indicates the values in the first 7 hr.

URINARY IODINE EXCRETION RATES

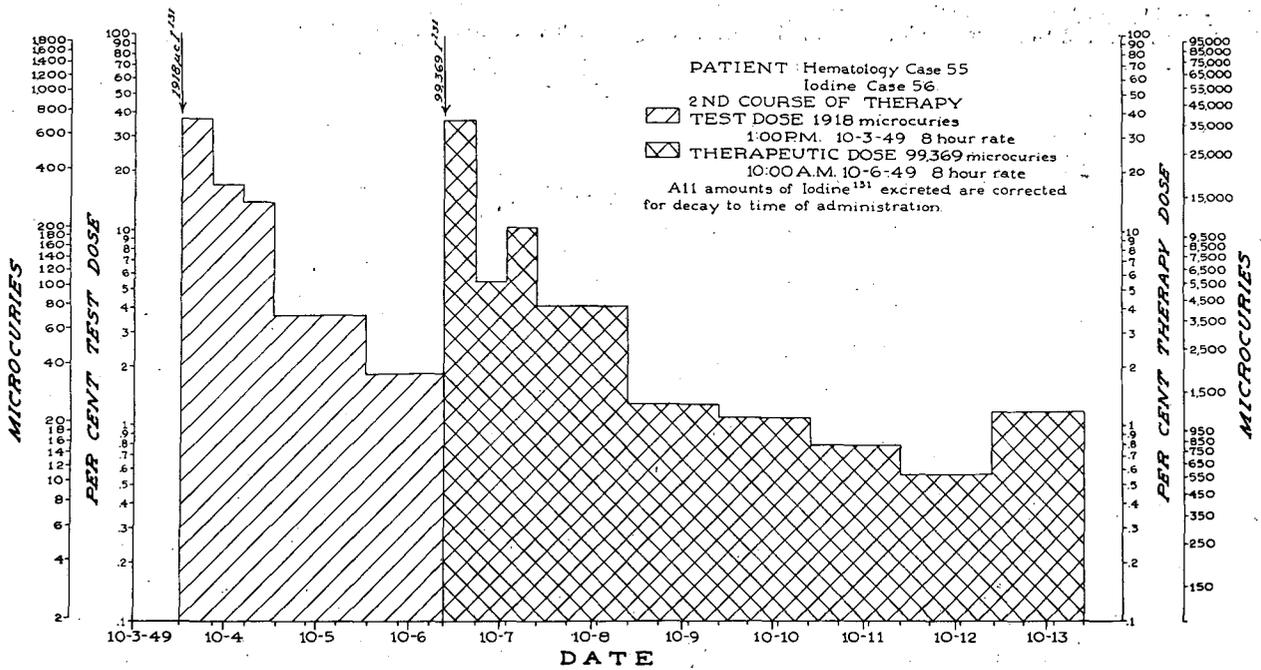


Fig. 14—Urinary iodine excretion in patient Hemat-55 Iod-56.

URINARY IODINE EXCRETION RATES

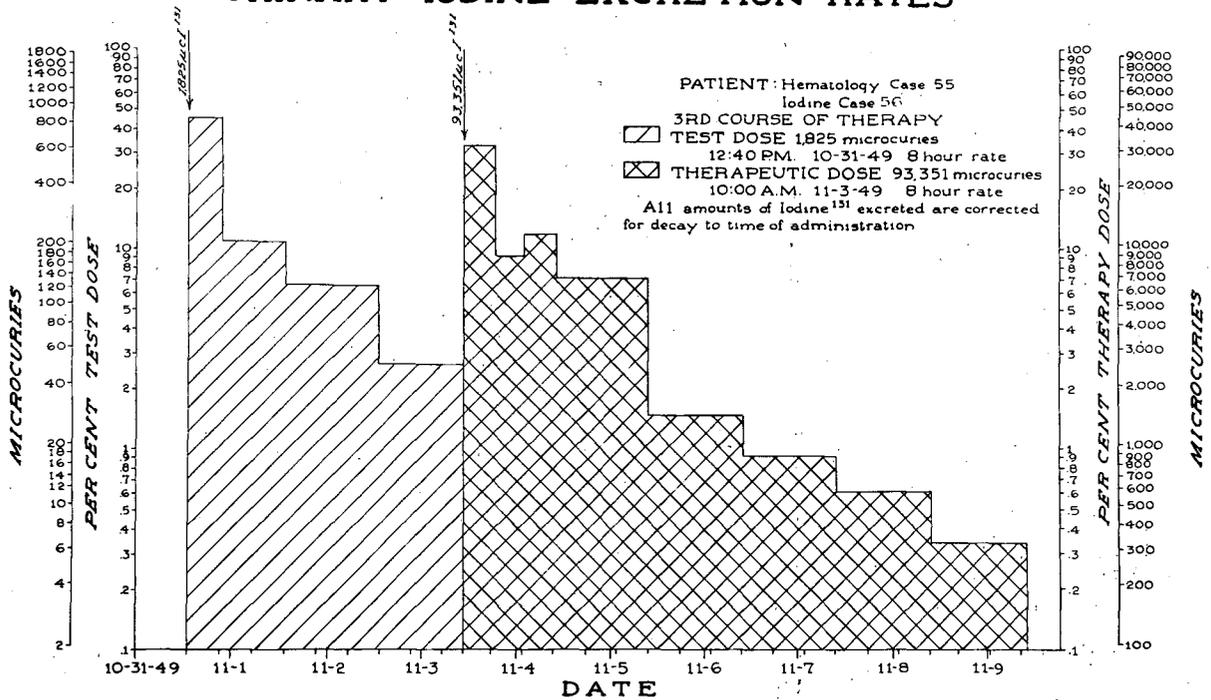


Fig. 15—Urinary iodine excretion in patient Hemat-55 Iod-56.

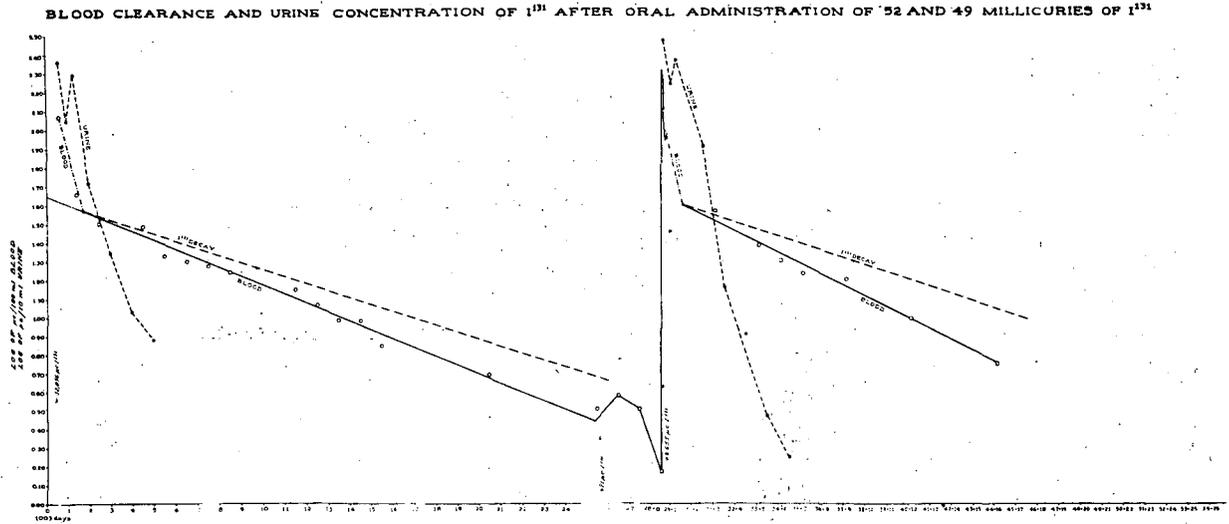


Fig. 16—Blood clearance and urine concentration of I^{131} in patient Hemat-55 Iod-56. The initial very steep slopes for both blood clearance and urine concentration extend over a period of 2 days, corresponding to a short biological half-life and are followed by a more gradual descending slope corresponding to a longer biological half-life. The physical decay curve drawn into the figure is to contrast the biological and physical half-lives.

URINARY IODINE EXCRETION RATES

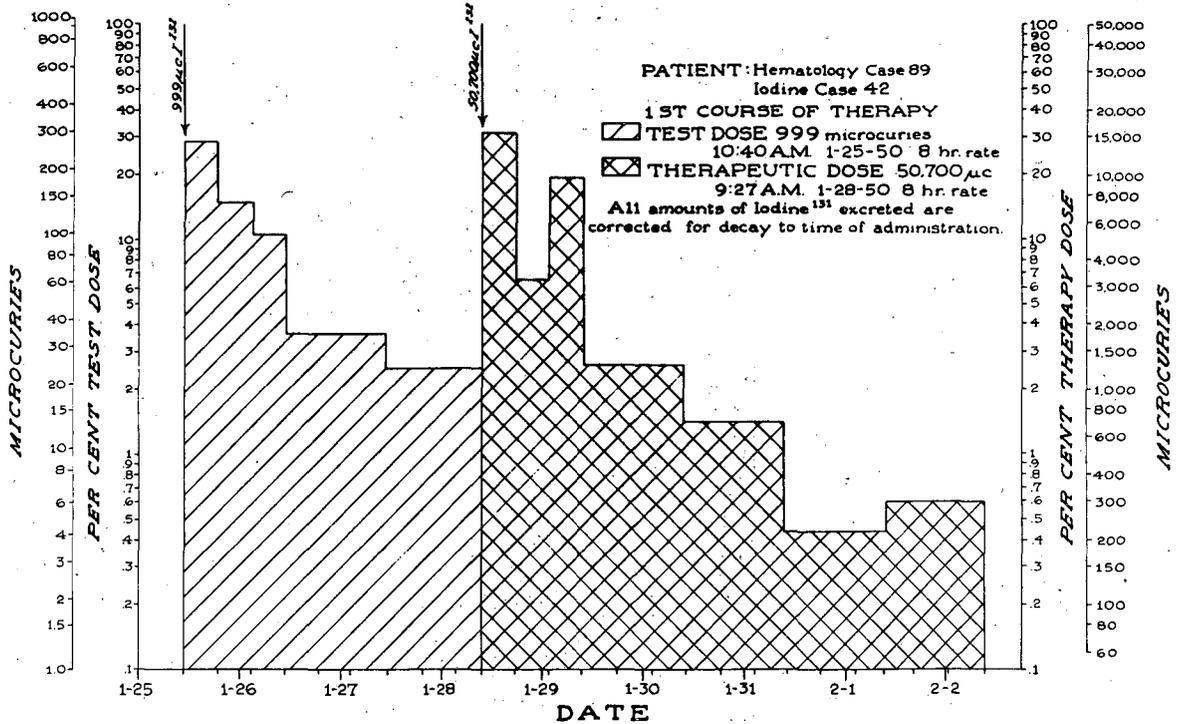


Fig. 17—Urinary excretion rate of I^{131} in patient Hemat-89 Iod-42.

URINARY IODINE EXCRETION RATES

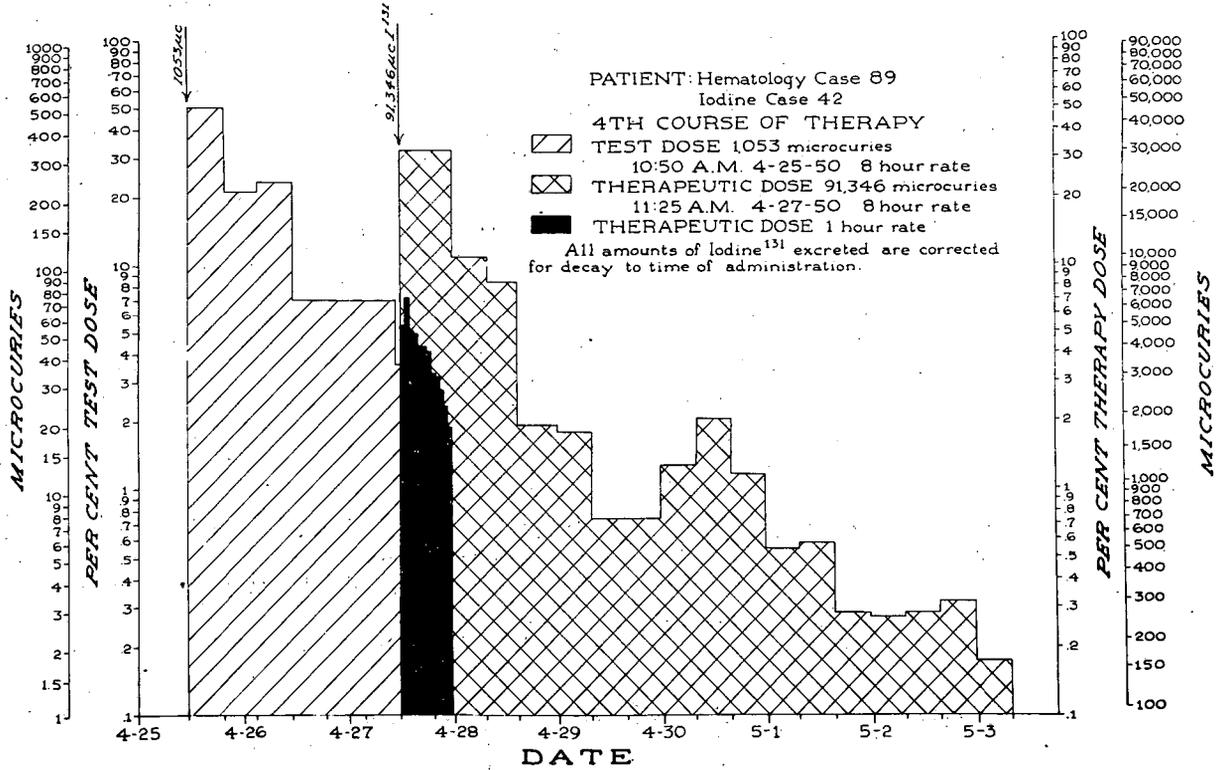


Fig. 18—Urinary excretion rate of I¹³¹ in patient Hemat-89 Iod-42.

URINARY IODINE EXCRETION RATES

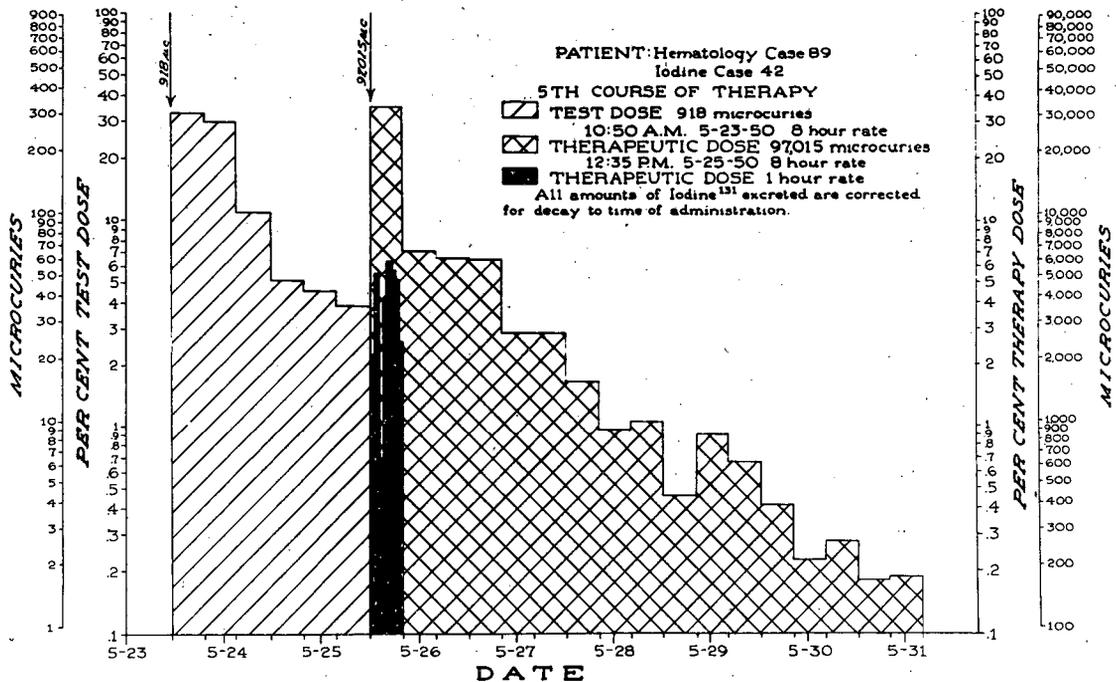


Fig. 19—Urinary excretion rate of I¹³¹ in patient Hemat-89 Iod-42.