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MEDICAL EFFECTS OF ATOMIC BOMBS

The Report of the Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan; Volume III.

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C O N T E N T S

Section 6
HEMATOLOGY

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A. Studies on the Circulating Blood.

Of the portions of the body that are accessible for examination, circulating blood is the one which is affected the earliest and the most profoundly by large amounts of ionizing radiation. It is, therefore, a sensitive and easily studied gauge not only of the severity of the effects of radiation but also of the character and degree of recovery. The principal handicap to an adequate presentation of the changes in the blood of Japanese injured by the atomic bomb is the fragmentary character of the data. Thus, although many counts are available, the majority are single counts on individuals. It is true that these were performed on all types of patients at every possible interval of time after the bombing but the fact remains that there were comparatively few serial blood counts on patients whose only injury was by gamma rays. Great as this handicap appears to be, it is minimized by the fact that very large numbers of patients were studied so that it is legitimate to treat the average blood counts of certain groups of patients that were made at varying periods of time. The fact that the average count in, say, the fourth week, was made on one series of subjects and the average count for the fifth week on another should not be considered a detriment. There were many patients similarly exposed and the employment of group averages seems a legitimate measure. So far as possible, the attempt will be made to deal with groups exposed to approximately similar quantities of radiation. This is not too important, however, because of the well-recognized individual variability. Accordingly, the general endeavor will be to discuss together patients who presented similar syndromes and thus allow inequalities in exposure to be neutralized so to speak, by inequalities in radio-sensitivity.

The material in this section will deal with the broad features of changes in the blood of persons exposed to gamma rays of the atomic bomb. It will deal mainly with counts and with the general pattern of the response as it was observed with the passage of time. The intricate interrelation and correlation of the blood picture with the symptomatology and with the factors of exposure (i.e., distance from the bomb) and protection (i.e., the sort of material intervening between the subject and the bomb) will be described in detail in the statistical section and in general in the clinical section. The effect of the gamma radiation on the morphology of the formed elements of the blood will be discussed here as will certain observations on the changes in the mechanism of coagulation of the blood.

Necessarily, much of the data for this section has been obtained from Japanese sources since the major changes in the blood picture had run their course by the time the Joint Commission arrived. In the employment of the Japanese material care has been taken to select data from organizations whose personnel were known by the American doctors and whose reliability was recognized. It is desirable at this point to acknowledge the work of those people, much of which was performed under unbelievably arduous circumstances. It would have been impossible to present a well-rounded picture of the changes in the circulating blood without the laboratory data which was supplied by the Japanese physicians.

On the basis of reports that have appeared in the medical literature since Heineke of Leipzig in 1903 (1) first described the action of Roentgen rays on the blood and blood-forming organs it was possible to anticipate the character of the changes in the circulating blood of the Japanese patients. The majority of the scientific articles describe the effects of various kinds of ionizing radiation on laboratory animals. A recent review of the effect of radiation on normal tissues by Dunlap and Warren (2) 1942 contains several statements which may help to orient the reader with respect to the data which is to be presented:

"When proper corrections for absorption are made, there is no convincing evidence at hand of qualitative or quantitative differences in the biologic effect of similar doses delivered at wavelengths within the range of soft and hard Roentgen rays, gamma rays, and the alpha and beta particles of radium."

(1) Heineke, H. "Ueber die Einwirking der Röntgen Strahlen auf Tiere" Münch. Medz. Woch. 50: 2099-2092, Dec. 1, 1903.

Idem., "Ueber die Einwirking der Röntgenstrahlen auf innere organ" ibid 51: 785-786, May 3, 1904.

Idem., "Experimentelle untersuchungen uber die Einwirking der Röntgenstrahlen auf des Knockenmark, nebst einingen Bemerkungen uber die Röntgentherapie der Leukämie und Pseudoleukämie und des Sarcomas." Deutsch Zeits. f. Chir. 78: 196-229, 1905.

Idem., "Experimentelle untersuchungen uber die Einwirking der Röntgenstrahlen auf innere organ." Mitteilungen an der Grenz, der Medz. u. Chir. XIV, Bd 1, u 2, 1904.

(2) Warren, S., Dunlap, C. E., "Effect of Radiation on Normal Tissues," III Effects of Radiation on the Blood and the Hemopoietic Tissues, including the Spleen, the Thymus and the Lymph Nodes," Arch. Path. 34: 562-608, 1942.

This is an important observation for it permits one to apply the information derived from the study of patients irradiated with ordinary hard Roentgen rays to the interpretation of the effects caused by the extremely hard gamma rays emitted by the atomic bomb. Furthermore, since there is still not too much information available on the effect of whole body Roentgen irradiation, the Japanese data may be applied vice versa. This last observation is supported by another statement from the review:

"Few concise data on the hazard of blood damage as an undesirable side effect of radiation therapy are accessible on the changes in the blood to be expected even from standardized radiologic procedures."

Whole or total body radiation with Roentgen rays of varying voltages has been practiced increasingly from 1932 and the effect of a single, relatively small (25-50 r) daily dose is found to be slight. There is no information available in the literature, however, on the largest single dose of total body irradiation that can be tolerated by man. Two other quotations, the first from the Review (2) and the second from a report by Minot and Spurling (3) will epitomize our current knowledge of the effects of ionizing radiation on the circulating blood:

"As a practical generalization, it may be said that sufficient irradiation of tissues with either radium or Roentgen rays will cause a reduction in the numbers of cells of all series in the circulating blood."

(3) Minot, George R., & Spurling, Roy G. "The effect on the blood of irradiation, especially short wavelength Roentgen ray therapy." Am. J. Med. Sci. 168: 215-241, 1924.

"The greater the dose, the more profound is the blood damage, the more rapidly it develops and the more slowly it is repaired. The blood response remains quite consistent qualitatively over a wide range of dosages although massive exposures may obscure some of the early changes and small doses sometimes fail to evoke the complete response."

It should be added at this point that the type of ionizing irradiation, the effects of which are described in the last two quotations, was hard Roentgen rays of an intensity of approximately 200 kilovolts.

With this background we may proceed to a consideration of, first, the changes in the circulating blood and, second, the changes in the bone marrow of the Japanese exposed to the gamma radiation of the atomic bomb. Presentation of the data will be simplified by discussing each of the affected elements of the circulating blood separately.

The clinical material on which this section is based has been selected from the large amount of data collected by the Joint Commission. The data have been chosen to provide the clearest picture of the changes in the peripheral blood consequent to gamma radiation of the whole body. The patients whose blood pictures will be described were of two general sorts:

(a) Patients with frank clinical evidence of the syndrome of radiation sickness. All these cases were studied by the Japanese and the data which are cited were collected by them and presented to the Joint Commission in the form of special reports by the individual groups of workers.

(b) Survivors, clinical data on whom were obtained in questionnaire form and submitted to analysis by the Joint Commission. All of the reports of the blood examinations performed on the members of this group prior to 1 October were provided by the Japanese physicians, but examinations subsequent to that time were conducted under the auspices of the Joint Commission. All the data from the questionnaires obtained from the survivor group were recorded in IBM cards, and are described in detail in the statistical section of the report. For the purposes of discussion in this section, one specially selected group has been used frequently, namely, subjects who were outdoors, unshielded, or indoors, inside a Japanese type building, and located within 1500 meters of the center of the explosion. This particular category has been chosen for discussion because there appears to be little question that the majority of the members of it received considerable amounts of gamma radiation from the explosion of the atomic bomb. In general, the effect of shielding and individual variations in radio-sensitivity will be over-looked in this section. The discussion will be concerned primarily with the blood picture in the various clinical stages of the syndrome of radiation injury. It is convenient to divide this syndrome into 4 types, the characteristics of which are shown in Table 1. Most of the patients of the first type died during a period when the hospitals and doctors were over-burdened and there are few data available on them. The majority of the patients studied by the Japanese during the latter half of August and the first half of September would be included in the second catebory; while the ones who survived and provided the bulk of the cases for the Joint Commission studies are the representatives of the last two types. The various elements of the blood will be considered separately.

(1) Erythrocytes and Hemoglobin.

The effect of the radiation emitted by the atomic bomb on the erythrocytes is complicated by the obvious factors of loss of blood due to wounds and to the hemorrhagic tendency that developed, as well as the familiary anemia associated with any sort of severe infection. Since it was not possible to collect large numbers of patients in each of the clinical classes as described in Table 1, who did not have complications of one sort or another, it is necessary to treat the patients as a group regardless of their other injuries. This consideration requires the reader to take a broad view of the data to be presented.

TABLE I

CLASSIFICATION OF CLINICAL TYPES OF THE SYNDROME OF RADIATION INJURY

	Very Severe	Severe	Moderately Severe	Mild
Approximate Mortality	100%	50%	Less than 10%	Nil
Time of Death, Weeks	1st-2d	3d-6th	6th-15th	-
Leukopenia	+ + +	+ + +	+ +	+
Purpura	+	+ + +	+ +	+
Epilation	±	+ + +	+	±
Ulceration & Inflammation of Mucous membranes	+	+ + +	+ +	±
Approximate distance from bomb, meters	Less than 1000	1000-	1000-1500	More than 1500

(1) Very Severe Group.

The results of the examination of the blood in 9 patients of this type from Hiroshima are shown in Table 2. All the patients had received some other injuries than that due to gamma rays and the extent of these injuries is difficult to determine from the record. Because of the familiar dehydration associated with burns, it is not desirable to attach much significance to the red cell counts in these early patients in whom loss of fluid from burns and from the commonly associated diarrhea occurred. The low color index in each case is remarkable and it cannot be explained readily on the basis of existing knowledge of the effect of ionizing radiation on the erythrocytes.

There are no data extant from either city on the reticulocyte count or the morphology of the red blood cells of the very severe cases. Inspection of the few blood films that are available (H-10645-1, Table 2; H-10619-I, Table 2) reveal that the microscopic appearance of the erythrocytes is quite normal. The same observation has been made by the Japanese physicians.

(2) Severe Group.

In many instances patients of this type were observed in well established clinics and followed over a period of from several days to several weeks, so that serial blood examinations are available in some instances. In the tables that follow typical examples are presented. (See tables 12 & 13.) The significant feature of the change in the red blood cell counts is the steady rate of decline which appears to reach minimum values at about the same time as the white blood cell count, which in many instances coincided with the death of the patient. As indicated in the classification, Table 1, approximately 50 per cent of the severe type of patients died. In Table 3 is listed the distribution of the red cell counts for two groups of Hiroshima patients who appeared to have been affected to the same extent by the gamma radiation. 25 died, and 27 survived. The degree of anemia is quite similar in the two groups and there is no clear evidence that this factor can be useful in prognosis.

TABLE 2

VERY SEVERE CASES (HIROSHIMA)*
EXAMINATION OF THE BLOOD**

CASE NO.	OTHER INJURIES***	Hb SAHLI %	RBC MILLIONS	WBC	DATE OF COUNT	DAY OF DEATH AFTER BOMBING
H-10614-I	B.W.	42	4.10	400	12 August	9
H-10619-I	B.W.	50	4.20	150	12 "	9
H-10645-I	B.	45	4.20	400	12 "	11
H-10615-I	B.	32	2.65	400	12 "	8
H-10616-I	B.	43	3.28	150	12 "	8
-	B.W.	40	3.75	250	12 "	-
H-10625-I	B.	40	4.13	400	13 "	8
H-10635-I	W.	40	2.82	300	12 "	8
-	W.	40	3.26	300	13 "	9

(All the patients were inside the Bankers' Club, Hiroshima, 200 meters from the center. See Section 1H)

*This data obtained from the report: "Hematological Study on the Atomic Bomb Disease," by K. Nakao, G. Kobayashi, S. Kato, Y. Yano, and M. Komiya; Medical Clinic (Dr. K. Sassa, Chief), Tokyo Imperial University.

**The blood counts were made by surgeons of Iwakuni Naval Hospital.

***B. = Burns; W. = Wounds.

TABLE 3

SEVERE CASES (HIROSHIMA)

DISTRIBUTION OF LOWEST RED CELL COUNTS DURING THE 3rd TO 5th WEEK AFTER BOMBING.

Patients Who Died	Range: Millions/mm^3	Patients Who Recovered
3	1.0 - 2.0	5
14	2.1 - 3.0	12
7	3.1 - 4.0	7
1	Over 4.1	3
25	Total	27

Color Index.

There is no consistent pattern of the variation of the color index which can be recognized in this type of patient. In individual cases, the index is seen to vary from less than 1.0 to values considerably in excess of even 1.5 and in the Nakao series of 25 fatal cases, the color index was 1.0 or greater in 17 cases and less than 1.0 in the remainder. The members of the Joint Commission have suspected that such variability is better explained by laboratory deficiencies than by some systematic change in the composition of the individual erythrocytes.

Price-Jones Curve.

Measurements were made of the mean diameter of the erythrocytes in stained blood films obtained from patients with the severe form of radiation injury. The number of examples is few but the general configuration of the curve is approximately normal which would suggest that good examples have been chosen. The values observed for the blood of patients obtained in late August in Hiroshima and in early September in Nagasaki are shown in Table 4. The first group of values (A. Hiroshima) are significantly different from normal in spite of the small number of subjects included in this group; and the low standard deviation suggests that the sampling was good. The second group (B. Nagasaki), because of the large standard deviation are not significantly different from the controls. Furthermore, the large standard deviation suggests that this group was not particularly representative. In the case of the third group (C Nagasaki) no standard deviations were supplied by the Japanese who performed the measurements but it is very unlikely that so small a difference between the means would be significant. The difference between the means of the patients and the means of the controls is only 0.14 microns which is smaller than the standard deviations of the most carefully studied group on record. In Price-Jones'(4) original monograph, the standard deviation for 100 normal subjects was 0.172 microns. The difference between the means for the normal studied by the Japanese and the normal for the means studied by the Joint Commission is to be explained on the basis of the type of micrometer and the technique used. In view of all these considerations, it appears that there is little change in the size of the erythrocytes of patients severely injured by the gamma radiation during the first four to six weeks after exposure.

(4) Price-Jones, Cecil, "Red blood cell diameters", London, Humphrey Milford, Oxford University Press, 1933.

TABLE 4

SEVERE CASES

Price-Jones' Curves

CITY	Number	MEAN DIAMETER OF ERYTHROCYTES MICRONS
A) Hiroshima (Smears made 3-4 weeks after bombing.)	6	7.02 ± .312
B) Nagasaki (Smears made 4-5 weeks after bombing.)	10	7.28 ± .610

Examinations of A) and B) performed by Joint Commission. Normal Control values obtained by same examiner; 7.44 .301 microns.

C) Nagasaki (Smears made 4-6 weeks after bombing.)	28	7.87

Examinations of C) performed by Japanese doctors, of I Medical Clinic, Kyushu Imperial University. Normal control value obtained by the same examiners: 7.73 microns

Reticulocytes

Only a few reticulocyte counts were performed in the severe cases. In the Nakao study there is an interesting difference between the distribution of reticulocyte percentage in the group of patients that died, and in the group that recovered. In Table 5 it can be seen that in the fatal group no patient had a reticulocytosis in excess of 0.4%; while among those who survived, one-half had values higher than that. The total number of subjects is unfortunately small, but the findings are consistent and are in agreement with other reports. The data suggest that reticulocytes may be equally as sensitive an indicator of the extent of damage to the bone marrow as the leukocytes or the platelets.

TABLE 5

SEVERE CASES (HIROSHIMA)

RETICULOCYTE COUNTS 3-4 WEEKS AFTER BOMBS.

Patients Who Died	Per Cent	Patients Who Survived
9	0 - 0.4	6
0	0.5 - 0.9	4
0	1.0 - 2.0	2
0	Over 2.0	1
9	Total	13

This finding of a low level of reticulocytosis in patients agrees well with the observations in animals irradiated experimentally in which a prompt and persistent decrease in the percentage of reticulocytes is characteristic, during the period of several weeks after exposure,

The morphology of the red blood cells as observed in stained blood films obtained during the course of the illness in severe cases appears essentially normal. There is no conspicuous degree of poikilocytosis but there does appear to be more than the usual variability in the size of the erythrocytes. In some of the blood films from patients severely affected by the gamma rays, nucleated red cells were seen during the acute phase of the illness. They were not found in every case, apparently, and when they occurred they were seen in small numbers, seldom more than 2-4 per 100 white blood cells. Those that were seen had an essentially normal appearance.

(3) Moderately Severe and Mild Cases.

The majority of these classes of patients survived and considerably more data are available on the pattern of the variations in their blood pictures. In these patients, as in the preceding groups, the characteristics of the response of the circulating blood was complicated by blood loss and the co-existence of severe infection. In this group, however, it is possible to observe such changes as may occur in the blood picture during the period of recovery.

Erythrocytes and Hemoglogin.

The case records selected by the Joint Commission and studied statistically were to a large extent of patients with the moderately severe and mild type of injury by gamma radiation. Changes in the blood picture of the group who survived are shown for each city in Table 6. The patients whose blood examinations are recorded were all located within approximately 1500 meters of the center. They were either outdoors, unshielded, or indoors, inside Japanese-type wooden buildings. It has been shown in the statistical study that subjects so situated were most affected by the bomb. This group contains the records only of patients who displayed symptoms to support a diagnosis of the syndrome of radiation injury. In the statistical study, no attempt was made to subdivide the clinical material on a basis comparable to the classification given in Table 1. Accordingly, it is inevitable that this group which we are taking as representative of the moderately severe, or mild type of the syndrome of radiation, will contain a certain number of patients of the "Severe" type who came under observation during their convalescence. The number of these whose blood counts are presented in this section is probably small, for two reasons. First, in the tables of average blood counts (see table 6) only the first blood examination is used. Since many of the severe cases had frequent blood counts, this type of patient will contribute only to the early weeks of the tabulation. Second, the group of subjects whose blood counts were used had a small incidence of high fever. One-fifth of those from Hiroshima and one-tenth from Nagasaki, respectively, had experienced fever in excess of 39°C. In general, nearly every one of the severe cases had high fever, so that the low total incidence of this symptom suggests that the severe cases were in the minority.

Upon inspection of Table 6, it is seen that the lowest values for hemoglobin and red blood cells occurred in the 6th and 7th week after the bombing. It is also seen that the average blood count has not returned to normal by the twelfth week. In Table 7, data collected from the clinics of the Kyushu University from patients who were exposed to the atomic bomb in each city are analyzed together and display the same sort of trend as is shown in the preceding table.

TABLE 6

MODERATELY SEVERE AND MILD CASES
EXAMINATION OF THE BLOOD
Mean Values for RBC, Hb and Color Index

HIROSHIMA Hb. Gms.	RBC Millions	Color Index	Weeks after Bombing	NAGASAKI Hb	RBC	Color Index
-	-	-	1	-	-	-
-	5.5*	-	2	-	-	-
9.3	3.9	0.7	3	6.8	2.7*	0.8
8.7	3.1	0.9	4	7.8	3.9*	0.6
8.8	3.1	0.9	5	9.1	3.7	0.8
8.0	3.1	0.8	6	8.9	3.5	0.8
8.3	3.0	0.9	7	7.4*	2.9*	0.8
9.0*	2.9*	1.0	8	8.3*	2.8*	0.9
7.7*	3.0*	0.8	9	9.9	3.2*	1.0
10.5*	-	-	10	9.5	3.3	0.9
11.0	-	-	11	9.4	3.6*	0.8
11.8	3.6*	1.0	12	10.0*	-	-
14.5	4.50	1.0	Normal Japanese	14.5	4.50	1.0

*Indicates that the mean is calculated on the basis of fewer than 10 cases.

TABLE 7

MODERATELY SEVERE AND MILD CASES (NAGASAKI)

KYUSHU IMPERIAL UNIVERSITY

Mean Values for RBC. Hb., and Color Index

SAWADA SERVICE 25			Number of Cases	MISAO SERVICE 16	
Hb.*	RBC	C.I.	Weeks after Bombing	RBC	C.I.
51	3.21	0.8	4	-	-
66	3.13	1.0	5	2.47	1.06
64	3.17	1.0	6	2.63	1.2
62	2.96	1.0	7	2.91	1.1
67	2.97	1.1	8	3.14	1.2
68	3.20	1.0	9	3.40	1.0
77	3.26	1.2	10	3.95	1.0
70	3.10	1.1	11	4.02	0.9
83	3.76	1.1	12	3.78	1.0

Color Index.

The tendency for the color index to approximate unity is shown in Tables 6 and 7. Because of reports in the medical literature of the development of hyperchromic, macrocytic anemia in subjects poisoned by radium, this condition was studied intently, particularly by the Japanese. In view of the fact that most infections as well as blood loss from wounds, should favor the production of an anemia with a color index considerably less than unity, the persistent finding of normal values for color index is, to say the least, suggestive of a tendency toward hyperchromasia in a purely relative sense.

*Hb - Japanese Sahli, 14.5 G = 100%.

MCV, MCH, MCHC

In one group of survivors in Nagasaki, careful blood counts and measurements of the packed cell volume were done. The average mean corpuscular volume, (MCV), mean corpuscular hemoglobin, (MCH), and mean corpuscular hemoglobin concentration, (MCHC), were estimated. The results of the study are shown in Table 8. In this table, the findings in 66 patients recovering from the effects of radiation injury are compared with two other groups of residents of Nagasaki City. The difference between the mean MCV of the group of patients, and of group A is statistically significant. The same is true for the difference between the mean MCH of the same groups. The tendency in the patient group toward macrocytosis and hyperchromasia is small; but it appears to be definite. As has been mentioned, this trend is of greater significance than the small numerical difference indicated, because it is observed in a group with infection, burns and wounds which would customarily cause the reverse type of change in the red blood cells. A sufficiently large group of patients with radiation injury, and without infection or other complications could not be obtained for study.

A. A group of 30 people who had never had any clinical symptoms of radiation injury. Most of these subjects were at distances greater than 3500 meters from the bomb.

X. A group of 55 people who lived in Kami-Nagasaki ration district, on the west side of the Nishiyama reservoir. These people were all completely protected from Gamma Rays by the high hills between them and the bomb. None had ever had any clinical symptoms.

TABLE 8

MCV, MCH, MCHC, (NAGASAKI)

	Number	MCV(1) Mean	MCV S.E.(4)	MCH(2) Mean	MCH S.E.	MCHC(3) Mean	MCHC S.E.
Patients	66	93.1	± 1.31	31.2	± 0.51	33.2	± 0.45
Group X	55	91.8	± 1.10	31.2	± 0.37	33.9	± 0.27
Group A	30	89.1	± 1.35	29.4	± 0.47	33.3	± 0.63
Normal(5)		87.0	± 5.00	29.0	± 2.00	34.0	± 2.00

(1) Mean corpuscular volume - cubic microns
(2) Mean corpuscular hemoglobin - gamma gamma
(3) Mean corp. hemoglobin concentration - percent
(4) Standard error of the mean
(5) Normal values for occidentals, from Wintrobe (loc. cit.). Comparable estimates for Japanese were not obtainable prior to the time of the American Occupation.

Price-Jones' Curve

Only one group of survivors known to have the syndrome of radiation injury in a moderately severe form was examined with respect to the mean diameter of the red blood cells. Blood smears from the patients in this group were collected in the Shinkozen Medical Aid Hospital and were measured carefully by Major S. Berg, MC, at the Army Institute of Pathology (see Figure 1). The results are shown in Figure 1 where the average Price-Jones' curve for 20 patients with radiation injury is compared with the average curve for Japanese normal controls. The comparison of the Japanese normal with the Price-Jones' normal is shown in Figure 3. The patients were selected for the study on the basis of the fact that they had either no, or very minor injury except that due to ionizing radiation. Unfortunately, infectious processes had been or were present in every case. The mean value for the red cell diameter of the irradiated group was 7.85 ± .428 microns, which is significantly greater than the control value of 7.44 ± .301 microns. The mean value for the patients suffering from the effects of irradiation was, statistically, significantly greater than the values for 2 other groups of subject resident in Nagasaki. One group (Series A) after careful clinical study, was found to have no evidence of radiation injury and the other group was composed of persons who were known to have been behind a large range of hills of such height that no gamma rays from the atomic bomb could have reached the residents (Series X). This region was in the Nishiyama section of the Kamin Nagasaki Ration District. (See Section 3N). The mean value for the red cell diameters of all these groups are shown in Table 9. (See also figure 2). The evidence from this study which may be assumed to be representative and to have been carefully done is that after injury by gamma radiation a tendency to macrocytosis in the peripheral blood is to be seen. The same observation as was made with respect to the color index and to the mean corpuscular volume, etc., applies to this situation. Since most of the patients undoubtedly had some infection which ordinarily would result in a microcytic type of anemia, the findings of an increased diameter of the red blood cell is certainly significant. (See table 9).

Reticulocytes

There are few studies of the reticulocyte counts of the less severely ill patients during the early weeks after the explosion. Considerably larger groups of reticulocyte counts, however, are available for the period of 8 to 12 weeks after the bombing. The observations made at this time are especially interesting because, as will be seen in the discussion of the bone marrow from survivors, this period during October was the time when erythropoiesis appeared to be the most marked. In Table 10 are shown reticulocyte counts on groups of comparable patients in each city. The most important feature of the tabulation is the uniformly low values observed. In each city, somewhat more than 50 per cent of the counts were less than 1 per cent, which may be considered as the ordinary normal value. This finding, when taken in relation to the range of the average erythrocyte count at the same time (see table 6), is very interesting. The values for the red cell counts in (8 - 12) those weeks are 2.9 to 3.6 million for Hiroshima and 2.8 to 3.6 million for Nagasaki, respectively. Regardless of the findings in the bone marrow, it is difficult to escape the conclusion that the delivery of young erythrocytes to the circulation is deficient. The degree of reticulocytes is certainly less than one would expect to find in patients with comparable degrees of anemia who were recovering from wounds and burns.

TABLE 9

MODERATELY SEVERE AND MILD CASES AND CONTROLS (NAGASAKI)
Mean Red Blood Cell Diameter

CLASS OF SUBJECT	NUMBER	MEAN AND STANDARD DEVIATION
1. Patients with Radiation Sickness	20	7.85 ± .428
2. Series A	10	7.61 ± .391
3. Series X	14	7.58 ± .287
4. Controls	9	7.44 ± .301
5. Normal Adults* (Wintrobe, loc. cit.)		7.5 ± .3

1) is significantly greater than 2), 3), or 4).

2) and 3) are not significantly different from each other, or from 4).

TABLE 10

MODERATELY SEVERE & MILD CASES

DISTRIBUTION OF RETICULOCYTE COUNTS
8 to 12 Weeks After the Bombing

A. Hiroshima (Nakao Series, Loc. cit.)

Per cent Reticulocytes	Number of Cases
0.0 - 0.4	6
0.5 - 0.9	7
1.0 - 1.9	9
Over 2.0	3
Total	25

B. Nagasaki (Omura Naval Hospital, Kaida Series)

Per cent Reticulocytes	Number of Cases
0.0 - 0.4	40
0.5 - 0.9	25
1.0 - 1.4	15
1.5 - 20	6
Over 2.0	11
Total	97

Morphology

The morphology of the red blood cells in the stained films of the patients with the moderately severe and the mild forms of the syndrome of radiation injury appears quite similar in the material from each city. There is more poikilocytosis and anisocytosis than was seen in the other types of material but even in the patients in this group it does not appear to be excessive. There was one major difference between the erythrocytes in the blood slides of the patients from the two cities. Punctate basophilia or stippled red cells were seen quite regularly in the Nagasaki study and were observed infrequently in the Hiroshima cases. In the latter city, the finding was encountered so seldom and was so apparently unrelated to other facts that there is insufficient data for tabulation. However, in Nagasaki, as can be seen in Table 11, it was found in a considerable number of cases and to a much greater degree in the patients with frank evidence of radiation injury. In the Table, it is evident that the incidence is higher in patients in the Omura Naval Hospital. The reason for this is uncertain. It may well be that the laboratory equipment there was better or that the technicians, having been warned to look for changes in the red blood cells, found more examples. The appearance of the stippled red cells differed in no way from those seen in persons who have had some lead absorption. (See figure 4). The number of stippled cells was never so great as that seen in the blood of patients with clinical lead poisoning. In some of the control subjects who said they were not in Nagasaki the day of the bombing an occasional stippled cell was found but there were never as many as could be seen in a typical patient. No facilities were available for investigating the likelihood that the water or the food contained lead in appreciable amounts. The finding is presented here without further attempt to interpret its significance.

Erythrocyte Sedimentation Rate.

This test is very popular with the Japanese physicians, and a great many determinations were made in all types of patient. Unfortunately, none of the data is suitable for critical analysis, since no corrections for the erythrocyte count are provided. Actually, in many cases, the sedimentation was apparently the maximum possible. The test was performed in febrile patients much more often than in afebrile ones, and there is no evidence to show that the results observed differed in any degree from what might be expected in any group of patients with serious infections.

Osmotic Resistance of Erythrocytes

A small number of determinations were made of the resistance of erythrocytes to hemolysis in hypotonic solutions of sodium chloride. Some of the patients studied were of the severe type, and some of the moderately severe or mild type. All the available reports are in agreement in finding no abnormality of the osmotic resistance of the red blood cells, of patients injured by gamma radiation.

TABLE 11

MODERATELY SEVERE AND MILD CASES (NAGASAKI)

Incidence of Stippled Red Blood Cells

A. Omura Naval Hospital

With Radiation Sickness	Total Patients	Without Radiation Sickness
204		177
49	With stippled Red Cells	9
24%	Per cent with Stippling	5%

B. Shinkozen Medical Aid Hospital

128	Total Patients	219
9	With Stippled Red Cells	-
7%	Per cent with Stippling	-

SUMMARY

1) In patients exposed to lethal and sublethal amounts of gamma radiation of the atomic bomb, the erythrocytes were seriously affected.

TABLE 12

SERIAL BLOOD STUDIES IN A TYPICAL FATAL

CASE OF THE SEVERE TYPE OF RADIATION INJURY

Hiroshima *

Date	Hemoglobin	RBC	WBC	Platelets
11 Aug.	70%	4.06	4200	203,000
20 Aug.	60%	3.37	1100	168,000
21 Aug.	65%	3.91	1000	-
23 Aug.	51%	2.05	350	-
25 Aug.	48%	1.69	170	-
27 Aug.	70%	2.68	120	-

DIFFERENTIAL COUNTS

Date	Metas	Stabs	Polys	Lymphs	Monos	Eos	Bas	NucReds
11 Aug.	2	30	44	20	4	-	-	-
20 Aug.	10	10	-	70	5	-	-	5
23 Aug.	-	-	-	(5)	-	(1)	-	-
27 Aug.	(1)	-	-	(1)	-	-	-	-

Numbers in parenthesis are absolute numbers; all others are percent

* Case 4, Nakao Report; Appendix 4H (5)

24 (6)

TABLE 13

SERIAL BLOOD STUDIES IN A TYPICAL NON-FATAL CASE OF THE SEVERE TYPE OF RADIATION INJURY

Nagasaki *

Date	Hemoglobin	RBC	WBC	Platelets	Reticulocytes
1 Sept	55%	2.50	2200	-	-
9 Sept	48%	2.24	600	17900	0 %
10 Sept	51%	2.26	1100	13560	0.2 %
14 Sept	41%	1.34	800	-	-
16 Sept	31%	1.48	1300	-	0.3 %
19 Sept	37%	1.59	1300	41300	0.5 %
24 Sept	29%	1.42	2800	76250	1.3 %
28 Sept	43%	1.40	4800	-	2.8 %
3 Oct	66%	1.78	5400	110000	4.8 %
8 Oct	62%	2.38	5600	238000	2.1 %
19 Oct	76%	2.72	9100	310000	2.2 %
27 Oct	79%	3.83	9100	318000	2.2 %

DIFFERENTIAL COUNTS

Date	Stabs	Polys	Lymphs	Monos	Eosinos
1 Sept	14.0	19.0	50.0	6.0	1.0
9 Sept	4.0	11.5	77.5	4.5	2.5
10 Sept	3.5	5.0	86.0	5.5	..
15 Sept	4.5	8.0	78.5	7.0	2.0
22 Sept	6.5	43.0	43.5	4.0	3.0
28 Sept	6.0	56.5	31.5	3.5	2.5
8 Oct	7.5	56.5	28.0	4.0	4.0
19 Oct	5.0	63.0	24.0	3.5	4.5
27 Oct	4.0	67.0	22.0	4.0	3.0

* Case S.K., 23, Male, Distance unknown,
Kusunoki Report, Appendix 4N (2)

2) The decrease in the total red cell count and total hemoglobin content began at once and in the severely affected cases reached critical levels in 3-4 weeks.

3) In the less severely affected persons, the maximum depletion of the red blood cell count occurred within 6 to 8 weeks.

4) The number of reticulocytes decreased markedly and this was apparently more so in the lethal cases than in those who recovered. Even when clinical recovery was well established, low values for the reticulocytes were the rule and levels that were in harmony with the degree of anemia observed were unusual.

5) At a time between the 8th and 12th week after the bombing when the marrow was found to display the maximum amount of erythropoietic activity, the reticulocyte count in approximately one-half the patients was still less than one per cent.

6) In general, the size and hemoglobin content of the erythrocytes of patients of all types was normal, or tended toward macrocytosis and hyperchromasia. It is pointed out that under the circumstances of blood loss, burns and infected states, the reverse would be expected in a group of similar size.

Leukocytes.

It is common knowledge among physicians that one of the earliest and most consistent effects of exposure of the human body to adequate amounts of ionizing radiation is leukopenia. The action of known lethal doses of X-rays and gamma rays on experimental animals has been studied and the rapid disappearance of leukocytes from circulating blood is a well recognized phenomenon. It is known that the rapidity of the decline of the white blood count is in general directly proportional to the size of the dose. Total body radiation of human subjects has been accomplished with modest doses of roentgen rays of the order of 25 to 75 r, but there is no available information on the effect of doses close to or exceeding the assumed lethal dose. In the case of the Japanese patients, irradiated at the time of the atomic bomb explosion, it is difficult to estimate the amount of gamma rays that they received, but there appears to be no question but that many received doses considerably in excess of the LD-50 (i.e., the amount of gamma rays that will cause the death of 50% of the subjects.) Accordingly, it is a matter of considerable interest to estimate the rapidity with which leukopenia developed in human beings.

White Blood Cell Count.

(1) Very severe cases.

Two series of cases, one from each city, are available for study. In Table 14 are listed all the white blood counts that were found in the records of the Omura Naval Hospital, of patients who died within 10 days of the bombing of Nagasaki. The location of these patients is not known, but the fact that all except two (Nos. 4740 and 4799) died of severe, extensive burns, indicates that they were probably in the open, unsheltered, and at least as close as 1,000 meters from the center. This tabulation is very important since it demonstrates the appearance of extreme leukopenia on 10 and 11 August, the first and second days after the bombing. In Table 15 are listed white blood cell counts from the records of the Iwakuni Naval Hospital, Hiroshima, Hiroshima. Practically all of these patients were inside the Bankers' Club (See Section 11H), a reinforced, concrete three-story building, 200 meters from the center. The earliest white blood counts in this group were performed on 10 and 11 August, the 4th and 5th days after the bombing. More extreme degrees of leukopenia were seen at this time as would be expected from the animal experiments. These two groups of patients provided the only reliable information that was obtainable on the rate at which the leukopenia developed in the most severely affected persons.

TABLE 14

VERY SEVERE CASES

LEUKOCYTE COUNTS - NAGASAKI

Data from Omura Naval Hospital

CASE NUMBER	DATE OF WHITE COUNT	W.B.C.	DATE OF DEATH
4739	10 August	2200	11 August
-	11 "	200-530	-
4733	10 "	1670	11 August
-	11 "	830	-
4737	11 "	1300-1600	11 August
4738	11 "	600-1000	11 August
4736	11 "	400-500	11 "
4740	11 "	530-1040	11 "
4734	11 "	830	11 "
4732	11 "	300	11 "
4731	11 "	715	11 "
4793	17 "	430-500	17 "
4799	18 "	1700	18 "
4795	18 "	500	18 "

TABLE 15

VERY SEVERE CASES

LEUKOCYTE COUNTS - HIROSHIMA

Data from Iwakuni Naval Hospital

Case Number	Date of White Cell Count	W.B.C.	Date of Death
H-10608-I	10 August	250	12 August
-	11 "	400	-
H-10634-I	12 "	120	12 August
H-10612-I	12 "	560	12 "
H-10604-I	11 "	1440	13 "
H-10606-I	12 "	840	14 "
H-10611-I	12 "	3400	14 "
H-10625-I	12 "	400	14 "
H-10620-I	12 "	2100	14 "
H-10618-I	12 "	2000	14 "
-	14 "	740	-
H-10635-I	12 "	30	14 "
H-10629-I	12 "	150	14 "
-	13 "	25	-
H-10609-I	13 "	50	15 "
-	14 "	37	-
H-10614-I	12 "	400	15 "
-	15 "	200	-
H-10640-I	13 "	560	15 "
-	14 "	490	"
H-10643-I	12 "	920	15 "
-	14 "	80	"
-	15 "	550	-
H-10626-I	14 "	100	15 "
H-10636-I	12 "	300	16 "
-	15 "	200	16 "

(2) Severe Cases

Patients of this type attracted considerable attention during the third to the sixth week after the bombing in each city where large numbers crowded the hospitals. During the height of this period it has been said that deaths from radiation sickness occurred at the rate of about 100 per day. The clinical syndrome was quite striking, with epilation, high fever, severe ulcero-necrotic lesions of the mucous membranes, and purpura. Many blood examinations were made, but often, unfortunately, these were single counts and the records of them frequently failed to show whether the patient lived or died. In the Nakao report (loc. cit.), however, the patients are classified on this critical basis and Table 16 has been prepared from that study.

TABLE 16

SEVERE CASES
HIROSHIMA

DISTRIBUTION OF LOWEST LEUKOCYTE COUNTS DURING THE 3rd TO THE 5th WEEK AFTER IRRADIATION.
Lowest Count only

FATAL CASES	W.B.C. DISTRIBUTION	CASES THAT RECOVERED
14	0-500	1
7	501-1000	8
4	1000-2000	10
0	over 2000	4
25	Totals	23

The leukocyte counts shown there are the lowest ones recorded which is not to say the lowest which occurred. It can be seen in general that leukopenia with total counts of less than 500 white cells per cubic millimeter was observed in the majority of fatal cases for in those who survived, the lowest recorded counts were of the order of 500 to 2000. A number of case records are available of persons with blood counts of less than 500 who recovered, but in general, it may be said that leukopenia of this extent indicated a grave prognosis. The typical distribution of the white blood cell count in a group of patients with the severe type of a syndrome of radiation injury is shown in Table 17, the data for which was collected in Nagasaki by a research team from Kumamoto Medical College between 4 and 8 September. All the patients in this group were acutely ill and it is regrettable that it is not known how many of them died.

TABLE 17

SEVERE CASES
NAGASAKI

DISTRIBUTION OF LEUKOCYTE COUNTS DURING THE
3rd-5th WEEK AFTER IRRADIATION
Lowest Count Only

PATIENTS WITH EPILATION	W. B. C. DISTRIBUTION	ALL PATIENTS
4	0-500	7
10	501-1000	17
10	1001-2000	15
5	over 2000	15
29	Totals	54

The table is of interest, however, since it shows the range of the total white cell counts in a group of seriously ill patients whose clinical symptomatology was generally similar. Furthermore, it is shown that in the group with epilation there was not a definitely greater incidence of leukopenia or a more severe degree of leukopenia than in the other groups. In Tables 12 and 13 are presented some characteristic serial blood counts from patients who survived and from others who died, showing the rate at which leukopenia and recovery (if it occurred) developed. The most interesting feature of these cases is the demonstration of how long the time-lag may be for the full development of the effect of gamma radiation of the bone marrow. The characteristic interval in persons who have received doses approximately the LD-50 appears to be from 14-35 days with the majority occurring in the third and fourth weeks.

(3) Moderately Severe and Mild Cases.

Just as in the case of the erythrocyte counts, many leukocyte counts were obtained from the less severely irradiated patients. Since this class was in the majority among the survivors it is natural that many of the blood exmainations of the Joint Commission were performed on them. In Table 18 are collected the average leukocyte counts by weeks for the most certainly exposed group of subjects (these people were within 1500 meters of the bomb, outdoors, unshielded, or indoors inside Japanese-type wooden buildings.) All had experienced the typical symptoms of the syndrome of radiation injury. The data show a very definite trend with the average for the minimum white blood cell count occurring during the fourth week after the explosion of the atomic bomb in each city. In spite of the small number of cases forming some of the weekly groups, the data from Hiroshima is especially illuminating since it shows the downward trend from the time of the explosion until the period of maximum depletion.

The rate at which the average leukocyte count increases during the recovery period is also shown in Table 18. It is interesting to note that the data collected by the Joint Commission is in close agreement with the average values for the leukocyte counts reported from two of the medical clinics of the Kyushu Imperial University where studies were made. (See table 19). This parallelism is significant since the successive weekly count in the Sawada Clinic and those of hospitalized patients in the Misao Clinic were performed on the same patients. The Joint Commission counts for one week, however, were not necessarily obtained from the same group of subjects as the counts of the previous week. The tempo of the recovery of normal values for the leukocyte count seems to be well established by this data. It may be stated on the basis of such study that after sublethal doses of gamma rays the leukocyte count decreases steadily for a period of 4 weeks; then, during the following 4 weeks returns to normal level.

TABLE 18

MODERATELY SEVERE AND MILD CASES

AVERAGE LEUKOCYTE COUNT IN EACH WEEK AFTER THE BOMBING

HIROSHIMA	WEEK	NAGASAKI
4200*	1	-
2400*	2	-
2400	3	5300*
1800	4	2500
2400	5	2700
3400	6	4700
5000	7	4800*
5300	8	8500*
6700*	9	8500
8600*	10	7100*
7400	11	7600
6800	12	5800*

*Average of less than 10 cases.

TABLE 19

NAGASAKI

MODERATELY SEVERE AND MILD CASES

AVERAGE LEUKOCYTE COUNT IN EACH WEEK AFTER THE BOMBING.

WEEK	JOINT COMMISSION	SAWADA CLINIC	MISAO CLINIC	
			ALL PATIENTS	HOSPITALIZED PATIENTS
1				
2				
3	5300			
4	2500	2700	2200	1800
5	2700	2700	3400	2200
6	4700	3300	4400	3500
7	4800	4500	4600	3600
8	8500	5600	4800	4800
9	8500	7200	5900	5200
10	7100	9600	6700	6200
11	7600	11000	-	-
12	5800	9400	-	-

Differential Counts.

(1) Very Severe Cases.

The members of the Joint Commission were unable to obtain any blood films of the severe cases from the Nagasaki hospitals. In his brief report, Surgeon- Lieutenant Shiotsuki (see appendix 4) mentions the differential counts of such patients and states that scarcely any cells except lymphocytes could be found, even after a prolonged search of the smears. Of the very severe cases from Hiroshima, records are available of 9 differential counts, and smears of two patients were given to the Joint Commission. The differential counts are listed in Table 20. It is apparant that there was no characteristic hemogram for this stage, and in a general way, the proportion of the various cell types was approximately normal, except for a shift to the left of the granulocytes and the presence of nucleated red cells in three of the nine examples. There does not appear to be any way in which such findings could be differentiated from other instances of severe leukanemia, as for example, acute benzol poisoning. The morphology of the few cells that remained in the blood with the exception of some of the polys, appeared normal to most examiners. In every case it is reported that giant neutrophiles were observed. Such cells were two or three times normal size and contained bizarrely shaped nuclei. In the smears obtained by the Joint Commission, such cells were also found. This type of giant neutrophil has been described as occurring in the blood of animals who have received large doses of X-rays.

Differential White Cell Count.

(2) Severe, Moderately Severe and Mild Cases.

The variations in the differential white cell counts were much more marked than the changes in either the red blood cell count or the white blood

TABLE 20

VERY SEVERE CASES

DIFFERENTIAL WHITE CELL COUNTS (after Nakao)
Absolute numbers in parentheses.

CASE NO.	NO. CELLS COUNTED	META-MYELOCYTES	STAB FORM	PODYS.	LYMPHS.	MONOS.	EOS.	BAS.	PLASMA CELLS	NUCLEATED R.B.C.
H-10614-I	50	0	20	40	28	6	0	0	2	0
H-10619-I	50	0	8	50	30	4	0	0	0	4
H-10645-I	50	0	16	60	14	10	0	0	0	0
H-10615-I	20	0	0	(12)	(1)	0	0	0	0	(7)
H-10616-I	13	0	(2)	(11)	0	0	0	0	0	0
–	100	4	26	56	8	4	2	0	0	0
H-10625-I	30	0	(1)	(22)	(5)	(2)	0	0	0	0
H-10635-I	20	0	0	(18)	(1)	(1)	0	0	0	0
–	50	–	10	70	16	2	0	0	0	0

36 (6)

See also Table 2

cell count and it is almost impossible to offer a general description of any characteristic pattern. When it is considered that both the lymphopoietic and myelopoietic tissues were affected, often to varying degrees, and when it is recognized that the radiosensitivity of these various tissues and even of different portions of the same tissue may differ, it is easy to understand how diverse the blood picture can be. The absolute numbers of all the formed elements of the blood were reduced and it is quite apparent that the degree of reduction of the several types of cells changed steadily. It is also apparent that these changes were independent of one another. Furthermore, it is seen in the section on the bone marrow and in the section on pathology that regeneration commenced to some extent in all the hematopoietic tissues during the first two weeks after exposure. The hemogram may thus be considered as reflecting, at any given time when an examination is made, a balance between the effects of destruction of the blood-forming organs and the effects of the degree of regeneration which has occurred. An inspection of the available differential counts reveals instances where the percentage of lymphocytes was as great as 70% to 90% and other cases where the percentage of neutrophils was as large as 80% in patients whose clinical symptoms were virtually identical. Other individuals displayed this amount of variation in the differential count in the course of one week. Under these circumstances it is preferable not to attempt to present any single average or usual pattern for the differential count. The medical reader will appreciate the fact that reduction to varying degrees of all the formed elements of the blood was the only characteristic feature of the severe form of radiation sickness. In Tables 12 and 13 are shown hemograms of typical cases which illustrate quite well the variable patterns that occur.

The tabulation of counts in Tables 21 and 22 however, displays some distinct trends and several interesting features. It is convenient here to present the results in severe cases at all stages, together with moderately severe and mild cases. The values shown in the tables are the averages of the first differential counts recorded on the Joint Commission questionnaires. The examinations made prior to the 7th and 8th week were transcribed from Japanese records. The patients whose counts are included all belong in "exposure groups A and B" (See Statistical Section). This class of subjects included anyone who was outdoors, unshielded; or indoors, inside a wooden building; and who was within 1500 meters of the center; plus those people who were in heavy buildings within 1000 meters of the center. The majority of these persons undoubtedly received sizable doses of gamma rays; and the fact that a differential count was made is reasonable evidence that that person displayed some evidence of radiation injury. Because of the small number of counts from patients whose location and shielding was adequately recorded, it is necessary to group together cases of differing severity.

In the tabulation of the average absolute differential counts, it may be seen that the average number of lymphocytes was less than normal throughout the entire period of 12 weeks after the bombing. The number of instances in each of several time periods where the absolute number of lymphocytes exceeded 2600 per cubic millimeter, the average normal value is shown for patients from each city in Table 23.

TABLE 21

HIROSHIMA

Average Differential Counts by Weeks;
Absolute Numbers and Percentage
Exposure Groups A and B

Week	Average WBC	No. of Cases	Stabs	Polys	Lymphs	Monos	Eos.	Baso
4	1000	11	40	325	575	55	10	1
5	2435	39	254	1093	883	104	30	5
6	3094	18	244	1392	1215	107	100	14
7	4113	22	770	1678	1152	364	122	16
8	5384	13	911	2309	1638	276	124	20
9	7320	10	247	4345	2012	557	236	-
10	6576	17	590	3332	1940	331	292	37
11	7048	66	602	3646	2048	343	340	25
12	6908	91	437	3594	2080	369	390	25
Normal absolute: aver:			154	3591	2660	350	252	35 *
Normal average : % :			2.2	51.3	38.0	5.0	3.6	0.5 *
4	1000		4.0	32.5	57.5	5.5	1.0	0.1
5	2370		10.7	46.1	37.3	4.4	1.2	0.2
6	3070		7.9	45.3	39.5	3.5	3.2	0.4
7	4100		18.7	40.9	28.0	8.9	3.0	0.4
8	5280		17.2	43.7	31.0	5.2	2.3	0.3
9	7400		3.3	58.7	27.1	7.5	3.2	-
10	6520		9.0	51.1	29.7	5.1	4.5	0.5
11	7000		8.6	52.1	31.0	4.9	4.8	0.4
12	6890		6.3	52.2	30.1	5.3	5.7	0.3

Total Cases 287

* Average of 28 normal Japanese males, September 1945, Misao , Appendix 4N (3)

TABLE 22

NAGASAKI

Average Differential Counts by Weeks;
Absolute Numbers and Percentage
Exposure Groups A and B:

Week	Average WBC	No. of Cases	Stabs	Polys	Lymphs	Monos	Eos	Baso
3	3310	7	611	917	1112	634	22	56
4	1550	12	145	538	704	104	21	14
5	3210	6	424	1706	913	110	70	4
6	--							
7	--							
8	7230	41	416	3795	2060	397	491	48
9	7900	137	353	4331	2044	509	569	31
10	7240	73	102	4124	2106	317	559	38
11	7940	67	88	4312	2487	379	636	30
12	7380	26	27	4017	2283	376	641	51
Normal absolute: average :			154	3591	2660	350	252	35 *
Normal average : percent:			2.2	51.3	33.0	5.0	3.6	0.5 *
3	3350		18.2	27.4	33.2	18.9	0.6	1.7
4	1530		9.5	35.2	46.0	6.8	1.3	0.9
5	3230		13.1	52.8	28.3	3.4	2.1	0.1
6	--							
7	--							
8	7200		5.8	52.7	28.6	5.5	6.8	0.6
9	7840		4.5	55.2	26.1	6.4	7.2	0.3
10	7240		1.4	57.0	29.1	4.4	7.7	0.5
11	7930		1.1	54.4	31.4	4.8	8.0	0.3
12	7390		0.3	54.4	30.9	5.1	8.7	0.6

* Average of 28 Normal Japanese males, September 1945, Misao, Appendix 4N (3)

TABLE 23

PER CENT OF DIFFERENTIAL COUNTS IN WHICH THE ABSOLUTE NUMBER OF LYMPHOCYTES WAS MORE THAN 2600
(Exposure Groups A & B)

HIROSHIMA	TIME	NAGASAKI
5.5%	2-6 weeks	0
20.3%	7-11 weeks)	20.4%
25.8%	12 plus ")	

After the 12th week in each city, an increasing number of absolute counts were found to be normal. It can be seen in the tables that there is some variation between the patients from each city. The lymphocytes of the Hiroshima group appear to have recovered less promptly than the ones from Nagasaki.

In the Tables 21 and 22 the trend toward recovery of the average number of granulocytes is seen to occur more rapidly than the lymphocytes. Thus, in the Nagasaki group, the average value for polys was in excess of normal (3900 per cubic millimeter) during and after the 8th week. In the case of the Hiroshima patients the polys were in excess of normal during and after the 9th week. The actual percentage of patients from each city whose absolute poly count was greater than 3900 in each of several time periods is shown in Table 24.

TABLE 24

PERCENTAGE OF DIFFERENTIAL COUNTS IN WHICH THE ABSOLUTE NUMBER OF POLYS WAS MORE THAN 3900
(Exposure Groups A & B)

HIROSHIMA	TIME	NAGASAKI
2.8%	2-6 weeks	9.4%
25.0%	7-11 weeks)	43.2%
34.6%	After 12 ")	

The average absolute numbers of the basophiles and the monocytes varied in approximately the same manner as the polys. The behavior of the stab forms has been disregarded in this discussion, because the average values for this type of cell were not reliable in this study.

It is quite apparent that a general reduction in the absolute numbers of each type of cell occurred after irradiation. This is the constant and conspicuous feature of the differential counts from all types of patients with clinical evidence of radiation injury. When the absolute values for the differential counts of a group of patients are averaged there is seen to be a fairly smooth progression of values. In the individual cases, however, the percentages often varied markedly from day to day. The situation illustrated in Tables 21 and 22 is quite representative, and there does not appear to be any reason to present any of the several small series of differential counts that are included in some of the clinical reports. All show the same trends, although none of the ones that are available give a clear indication of the length of time required for the average lymphocyte and poly count to return to normal levels.

Among the interesting features of these tables are the serial changes in the percentage of eosinophiles in the differential counts. Individual instances were observed where the eosinophile count was as high as 68% and in many cases the values were in excess of 20%. There is no apparent reason for the occurrence of higher degrees of eosinophilia in the patients from Nagasaki as compared with those from Hiroshima. The eosinophilia was studied by Ueda and Nikaido at the Shinkozen Medical Aid Hospital in October and November (Appendix 4N, 25). The differential counts of all the patients examined were divided into 2 groups: Those with more than 10% eosinophils, and those with less. The results are shown in Table 25. It can be seen that the incidence of eosinophilia in excess of 10% was greatest in the group with the clearest evidence of radiation injury. It is shown in the section of the bone marrow that in many of the tissues obtained during October (i.e., 8th to 12th week), eosinophilia was a common finding. The significance of this temporary condition is not known. Studies of patients receiving Roentgen therapy have shown blood eosinophilia frequently. There is general agreement in the reports in the literature that the proportion of these cells may range from 10 to 25 per cent during the period of several weeks after treatment. The reasons for the larger percentages in the bombed patients remains to be determined.

TABLE 25

NAGASAKI

MODERATELY SEVERE AND MILD CASES
Incidence of Blood Eosinophilia

TYPE OF PATIENT	NUMBER	EOSINOPHILIA IN EXCESS OF 10% Number	EOSINOPHILIA IN EXCESS OF 10% Per Cent	MAXIMUM EOSINOPHILIA OBSERVED Per Cent
Radiation injury with epilation.	50	38	75	39%
Patients without epilation.*	297	130	40	54%
Uninjured residents of Nagasaki	50	20	40	22%
Controls from outside the city.	15	3	20	14%

*Some of these patients had clinical evidence of radiation injury, others had "only" wounds and/or burns. The tabulation is unsatisfactory because precise criteria for the diagnosis of radiation injury had not been formulated.

MORPHOLOGY

The most constant abnormality of the morphology of the leukocytes on the stained blood films of patients with the syndrome of radiation injury during the period of recovery was seen in the neutrophils. Marked toxic granulation and even occasionally toxic vacuoles were observed. This finding can undoubtedly be attributed in part to the infections which occurred in almost all patients. As might be expected, a progressive shift to the right was seen as recovery progressed. The failure of this to occur or the persistence of the left shift of the early stages was observed in patients whose convalescence was protracted or unsatisfactory.

The ordinary lymphocytes of the blood: the small, medium-sized and large forms, did not display any morphologic alterations. An abnormal-appearing lymphocyte, however, was seen in a considerable number of the cases. This cell had the general appearance of the atypical lymphocytes which are seen in infectious mononucleosis. It was large with a variable type of cytoplasm, some had abundant, non-granular, palely basophilic cytoplasm which tended to stain a deeper blue at the margin. In others the cytoplasm was more generally basophilic, often flocculent and in some cases contained vacuoles and azure-filled granules. The nucleus was comparatively small in relation to the size of the cell, was excentrically located, and was rarely indented. The chromatin was arranged in rather coarse bundles and there was little contrast in color between it and the parachromatin. The general appearance of the nucleus was homogeneous and nucleoli were rarely seen. A similar type of cell was observed in smears of marrow obtained at biopsy in approximately one-half of the preparations from Hiroshima and one-third of the preparations from Nagasaki. In one series of cases where the percentage of these abnormal lymphocytes was recorded, they were observed in the blood smears of approximately one-fourth of the patients. The details of the observation are shown in Table 26. In this table the group labeled "No Radiation" was formed on the basis of tentative criteria used during the study in Japan. Since more than two-thirds of these patients were severely burned, as shown by the fact that they were still in the hospital in October, the presumption is strong that many of them were examples of the moderately severe or mild form of radiation sickness. In a group of over 50 control subjects no cells of the type referred to here as abnormal lymphocytes were seen. Typical examples of the abnormal lymphocytes are shown in Figures 4, 5 and 6. The significance of the finding of these cells is not known with certainty. In view of the presence in the bone marrow, spleen and lymph nodes of similar cells, it is not unexpected.

TABLE 26

NAGASAKI

RECOVERING SEVERE: MODERATELY SEVERE: MILD CASES

INCIDENCE OF ABNORMAL LYMPHOCYTES IN THE STAINED BLOOD FILM

NUMBER OF PATIENTS		NUMBERS WITH ABNORMAL LYMPHOCYTES
With diagnosis of Radiation Sickness	204	66
With no diagnosis of Radiation Sickness	177	29
Totals	381	95 -25%

Monocytes were normal in appearance. It was a matter of some interest that monycytosis was not observed. It was expected by some of the observers, who reasoned from analogy with the agranulocytic angina of the Schultz type where monocytosis is a distinctive feature of the recovery stage. An occasional histocyte was seen in some of the blood films, one example of which is shown in Figure 6. In view of the large number of these cells in the marrow, the escape of a few into the blood is not unusual.

Plasma cells were seen in many instances but usually in small numbers, one or two per 100 white blood cells. These cells also were present in large numbers in the marrow, spleen, lymph nodes and other tissues of the irradiated patients, and the appearance in the circulating blood of small numbers of them should occasion no surprise.

SUMMARY

After exposure to injurious amounts of gamma radiation, the leukocytes of the circulating blood undergo a typical series of changes:

1. In the patients who received definitely lethal doses of gamma rays, a leukopenia of 1000 per cmm or less may be apparent within 24 to 36 hours and become progressively more marked until death. The white cells may completely disappear from the circulation and white cell counts of less than 500 per cmm were the rule.

2. In patients who received amounts of gamma rays which approximate the LD-50 (the more severe cases of the classification in Table 1), the leukocyte count declined slowly after irradiation and reached the minimum level during the 3rd to 4th weeks. In the fatal cases the counts fell to less than 500 per cmm in more than one-half of the patients before death occurred. In those who survived, the depletion was less profound and counts below 500 were observed

in only a few patients. In the survivors the lowest white counts generally occurred in the fourth week.

3. In the patients who received definitely sublethal doses of gamma rays, the leukopenia occurred but the average count in the 4th week, when the lowest level was reached, ranged from 1500 to 2500 per cmm. In this type of patients, white cell counts below approximately 1500 were not seen.

4. The length of time required for the white count to return to normal levels was about 4 weeks on the average for the patients of either class who recovered.

5. The differential count revealed that lymphocytes were reduced in absolute numbers from the time of the first observation (2-4 weeks) until approximately the 12th week. The polys were also reduced in absolute numbers from the onset until approximately the 8th-9th week when the average value returned to normal. A shift to the left of the granulocytes was present early in the course of the disease.

6. There was no blood picture which could be called pathognomonic for any stage of the disease.

7. The average percentage and the absolute numbers of eosinophils increased during the 8th-12th week; and percentages as high as 68% were reported.

Blood Platelets.

The amounts of X-rays that are used in therapy seldom have any serious influence on the number of platelets in the circulating blood although occasional cases have been reported where a thrombocytopenic purpura was apparently produced. In experimental animals only a few investigators have observed a marked or prolonged effect on these elements. In one series of experiments with dogs exposed to an amount of Roentgen radiation, approximately equivalent to twice the LD-50 for dogs, (1) the platelets were virtually eliminated from the blood and purpura was commencing at the time of death, 7 to 11 days after irradiation. In human beings receiving Roentgen therapy, the platelet count is frequently considerably increased a week or two after treatment and for this reason some radiologists have used X-rays in the treatment of thrombocytopenia of various sorts. Because of the small amount of information in the literature on the behavior of thrombocytes in subjects receiving large doses of ionizing radiation, the changes which occurred in the Japanese were of considerable interest.

(1) Very Severe Cases.

Platelet counts were recorded for only 2 of the cases of this type studied in Hiroshima. They were both made on the 6th day and were performed on patients who died on the 8th and 9th days respectively. The total number of platelets per cmm were: 87,400 and 64,500. Cutaneous purpura was not present in either case. Among 20 patients in one series with the very severe form of the syndrome of radiation sickness who died during the first 10 days after the bombing, cutaneous purpura was recorded in only one. The amount of purpura evident in the viscera at autopsy, however, was variable and was seen with different frequencies in the various autopsy series from

(1) Shonse, Warren & Whipple, loc. cit.

each city.

(2) Severe Cases.

Extreme thrombocytopenia was one of the striking characteristics of the syndrome in the severely affected patients. The most useful data on the occurrence of this finding is included in the Nakao report. In the group of fatal cases, platelets were counted at some time in the period of the third to the sixth week in 14 of the 25 patients, (see table 27). Twelve of the 14 were found to have fewer than 25,000 platelets per cmm. In the group of 29 non-fatal cases of the severe type, platelet counts were performed on 24 during the same time period. Five of these 24 counts were lower than 25,000 per cmm. The distribution of all these counts is shown in Table 28. Among the patients with the severe type of radiation injury studied at the Kyushu Imperial University (Kusunoki Clinic) 11 of 17 had platelet counts less than 100,000; and 7 of 17 were less than 25,000. The 4 fatal cases were in this latter group.

A severe hemorrhagic state with purpura, melena, epistaxis, hematuria and metrorrhagia developed in many of the patients. This situation is described in detail in the clinical section. It is unfortunately true that any attempt to demonstrate a relationship between the degree of thrombocytopenia and the hemorrhagic state is hampered by the fact that in general platelet counts were only performed on patients with purpura. There is no doubt that patients with purpura had thrombocytopenia, but there is no large amount of data on the platelet counts of irradiated patients who did not have clinical purpura. It seems reasonable to say that the hemorrhagic manifestations were associated with, or occurred concurrently with the thrombocytopenia. It is not possible to state the degree of thrombocytopenia which was invariably associated with purpura; or for how long a period of time thrombocytopenia existed before the appearance of purpura.

(3) Moderately Severe or Mild Cases.

The rate of return of the platelet count towards normal cannot be cited for any group of patients but a number of series of cases are available where platelet counts were made at different periods of time after the bombing. There is a high degree of variation in the results, part of which may be due to the technical methods used and part of which is undoubtedly explainable on the basis of the sampling. The case records, (See table 12 and 13) give one a fair idea of the rate of recovery in typical instances. In Table 29 are listed 4 series of patients showing the percentage of cases in which the platelet counts were less than 150,000 (approximately one-half the average normal values) at the time of the study. The values for the Sawada Clinic are open to question for it was observed that all the thrombocyte counts performed there were approximately 50 per cent higher than the usual values. The other series are probably quite reliable. Distribution of blood platelet counts for the Hiroshima series for October and November is shown in Table 30. In Table 31 the averages for platelet counts performed in the Omura Naval Hospital in October and November (10 to 15 weeks after the bombing) on 3 classes of patients are listed. The tabulation demonstrates that in persons with definite radiation sickness the average number of thrombocytes is less than in the group of patients convalescing from wounds and in whom there was some doubt whether they had ever been injured by the gamma radiation. None of this injured group had been burned or had epilated. None had been found to have white counts less than 4000 and none had ever experienced any of the characteristic symptoms of radiation sickness. In spite of this, it is apparent that the mean platelet count in this group is less than one would expect in a group of wounded persons. A hemorrhagic tendency occurred in the moderately severe and mild types of cases but to a less striking extent than in the severe group. The details of the purpuric manifestations in this sort of patient are presented in the clinical section.

(4) Morphology.

There do not appear to be any changes in the morphology of the blood platelets in the patients with gamma ray injury.

SUMMARY

1. After exposure to large doses of gamma rays, the blood platelets are decreased in number.

2. Thrombocytopenia was present to a significant degree within one week.

TABLE 27

SEVERE CASES, FATAL

BLOOD PLATELET COUNT PER mm^3

(HIROSHIMA)

	3rd to 6th week
4200	15,800
4500	22,900
5200	23,000
7700	23,200
8800	34,200
10400	68,200

TABLE 28

SEVERE CASES, NON-FATAL

DISTRIBUTION OF BLOOD PLATELET COUNTS

(HIROSHIMA)

	3rd to 6th week
Less than 50,000	11*
50,100-100,000	5
100,100-150,000	5
150.100-200,000	1
More than 200,000	2
Total	24

*5 of these counts were less than 25,000/mm^3

52 (6)

TABLE 29

CONVALESCENT SEVERE, MODERATELY SEVERE AND MILD CASES

INCIDENCE OF PLATELET COUNTS BELOW 150,000

DATE OF STUDY	PLACE	NO. EXAMINED	NO. WITH PLATELETS BELOW 150,000	%
15-30 September	Nagasaki (Sawada Clinic)	18	3	36
October-November	Hiroshima	28	16	57
October	Nagasaki (Omura Naval Hospital)	90	34	38
November	Nagasaki (Omura Naval Hospital)	66	16	25
	All October, November Cases	184	66	36%

TABLE 30

CONVALESCENT SEVERE, MODERATELY SEVERE AND MILD CASES

DISTRIBUTION OF BLOOD PLATELETS IN OCTOBER AND NOVEMBER

HIROSHIMA

Less than 50,000	2
50,100-100,000	8
100,100-150,000	8
150,100 - 200,000	5
Over 200,000	5
Total	28

TABLE 31

CONVALESCENT SEVERE, MODERATELY SEVERE, AND MILD CASES

AVERAGE PLATELET COUNTS, OCTOBER - NOVEMBER
OMURA NAVAL HOSPITAL

NAGASAKI

CLASS OF PATIENT	NUMBER	BLOOD PLATELETS AVERAGE COUNT
1. Radiation Sickness only*	11	187,000
2. Radiation Sickness plus burns and/or wounds	90	176,000
3. Wounds only**	55	213,000

*These patients had no other injury except by gamma rays.

**These patients were all inside heavy buildings and the majority were farther than 1500 meters from the bomb. None had burns or any characteristic symptoms attributable to gamma ray injury.

BLEEDING TIME, CLOTTING TIME, AND CAPILLARY FRAGILITY.

(1) Very Severe Cases.

There are no records available of the bleeding time and clotting time of patients who died during the first two weeks after the bombing. In some of the clinical records there is evidence that a hemorrhagic tendency was developing in this class of patients. In a group of 20 patients of this type only one developed purpura prior to his death.

(2) Severe Cases.

The severe purpura that occurred in cases of this type prompted the attending physicians to measure the bleeding time and the clotting time in many instances. Unfortunately, much of the data were incomplete and were not suitable for analysis. An adequate investigation of any patient with a hemorrhagic state should include the following tests, if a precise diagnosis is to be made:

1. Bleeding time.
2. Clotting time.
3. Prothrombin time.
4. Description of the retraction of the clot.
5. Estimation of plasma fibrinogen, total plasma protein, serum calcium and plasma ascorbic acid.
6. Determination of capillary fragility by the Rumpel-Leede's method, or by some vacuum method of producing petechiae.

There are no case records available where all those studies were performed on a single patient, or even in a small group of patients. Actually, all the tests except the prothrombin time were performed on some series of patients, so that a composite result is available. The chemical studies were performed on a mixed group of convalescent severe cases, and convalescent moderately severe cases and will be mentioned in the appropriate section.

A series of cases which illustrate the features of the hemorrhagic state is shown in Table 32a. These patients were studied by a group of hematologists from Kumamoto Medical College and were selected for study on clinical grounds.

TABLE 32a
NAGASAKI
N
SEVERE CASES - 4-8 SEPTEMBER

STUDY OF HEMORRHAGIC TENDENCY
Total White Cell Count: Less than 1000

RUMPEL-LEEDE'S	BLEEDING TIME	CLOTTING TIME	W.B.C.	EPILATION
+	28'00"	13'30"	100	+
+	23'00"	12'30"	250	-
+	30'00"	16'30"	350	+
+	13'30"	13'30"	550	+
+	30'30"	15'00"	550	+
+	22'30"	15'30"	850	-
-	20'00"	12'30"	300	-
-	17'00	15'00"	500	+
-	16'00"	14'00"	650	-
-	24'30"	- -	650	+
-	19'30"	20'30"	675	+
-	26'30"	10'30"	800	+
-	20'00	8'30"	850	-
-	3'30"	- -	900	+
	White Cell Count: 1000 - 2000.			
-	16'30"	- -	1050	-
-	11'30"	12'30"	1450	+
-	6'30"	12'30"	1700	+
-	10'00"	14'00"	1900	+
-	4'30"	11'30"	1900	+
	White Cell Count: 2000 - 3000.			
-	8'30"	13'00"	2400	-
-	7'00"	9'00"	2500	-
-	5'00"	13'00"	3000	-

Only the most severely affected were included in this group. The special tests were carefully performed. The Rumpel-Leede's phenomenon was sought after a tourniquet had been applied for 3 minutes. Bleeding time was measured by Duke's Method, and the normal value for Japanese was said to be from 3-5 minutes. Clotting time was measured by the Sahli-Fonio method; and normal values in Japanese range from 6-10 minutes. Unfortunately, platelete counts were not made on this group; but the reader may recall the distribution of low values in Tables 27 and 28 where 15 of 36 cases had platelet counts of less than 25,000 per cubic millimeter; and only 3 of 36 were higher than 150,000. Table 32a illustrates the marked variability of the various factors, as well as the important facts that both the bleeding time and the clotting time are prolonged; and that the Rumpel-Leede's phenomenon does not appear to be closely related to any single factor. In Table 32b examples of the measurements of bleeding time of patients in the Ono Hospital, Hiroshima. This tabulation demonstrates the inconstant character of the changes in bleeding time.

TABLE 32b
HIROSHIMA

SEVERE CASES 30th - 34th DAY
Study of Hemorrhagic Tendency

Total White Cell Count: Less than 1000.

BLEEDING TIME	WBC	EPILATION	CAPILLARY RESISTANCE*
16'30"	540	-	
2'30"	600	+	
15'30"	625	-	
6'00"	850	-	
White Cell Count: 1000-2000.			
4'30"	1050	-	
2'00"	1100	-	-180
7'00"	1200	-	
2'00"	1425	-	-250
4'30"	1600	-	-240
3'30"	1900	+	
3'30"	1950	-	-270
White Cell Count: 2000 - 3000			
4'00"	2040	+	
3'30"	2240	-	
6'00"	2850	+	
12'00"	2300	-	
2'00"	2475	-	-240

*In mm Hg negative pressure, to produce petechiae.

An interesting study was made in the I Medical Clinic, Kyushu Imperial University, where the hemorrhagic tendency in 7 patients with the non-fatal form of severe radiation injury was tested serially over a period of 5 weeks. In this clinic the clotting time was measured by the capillary tube method, normal values for which were said to be 3'00 to 4'00. The results are shown in Table 33.

TABLE 33

NAGASAKI
SEVERE CASE

STUDY OF THE HEMORRHAGIC TENDENCY (7 Patients)

			AVERAGE VALUES		
WEEK AFTER BOMBING	PLATELETS	BLEEDING TIME	CLOTTING TIME	CAPILLARY FRAGILITY	
				INFRACLAVICULAR REGION	INNER ASPECT OF ARM
4	105,000	12'45"	6'30"	16.0	16.5
5	81,300	8'20"	6'45"	17.3	16.6
6	90,800	4'00"	5'30"	18.8	19.6
7	82,000	2'45"	5'15"	22.0	22.2
8	75,000	3'00"	4'30"	23.5	23.5
Normal. .	(250,000	2'00"	3'00"	-	(more than
	(300,000	3'00"	4'00"	Approx.	(25-26

The capillary fragility was measured by a vacuum device, and the results are recorded in units of negative pressure, presumably centimeters. In this group of patients, only 1 of the 7 had a positive Rumpel-Leede's test.

There is no question of the fact that a hemorrhagic state was a characteristic feature of the severe type of the syndrome of radiation injury. Unfortunately, the clinical laboratory data which are available were not sufficiently adequate to permit a description of the degree of abnormality of the various tests, which might be used in studying such states. It is also not possible to characterize accurately the type of purpura which developed in the irradiated patients. Accepting the incomplete information at its face value, there appears to be a close resemblance to the so called toxic or secondary thrombocytopenic purpura.

(3) Moderately Severe and Mild Cases.

Even less reliable information is available on the less severely affected patients. The records frequently include reference to the occurrence of petechiae or to gingival bleeding but there are few systematic reports of laboratory studies. By the time the Joint Commission arrived, no instances of purpura were observed except in moribund patients, most of whom were dying from infection of some sort. One group of 12 patients were studied in the Misao Clinic. These were classified as "average" on the basis of the fact that the symptoms were less severe and appeared somewhat later after the bombing than was the case with the patients listed in Table 34. The average blood counts in this "average" group in the 5th week after the bombing were:

Hgb - 68%; RBC - 3.09 million; WBC - 1870; Platelets - 150,000; Reticulocytes - 0.5%.

TABLE 34

AVERAGE CASES (NAGASAKI)

STUDY OF THE HEMORRHAGIC TENDENCY (12 Patients)

WEEK AFTER BOMBING	PLATELETS	BLEEDING TIME	CLOTTING TIME	CAPILLARY FRAGILITY INTRACLAVICULAR REGION	CAPILLARY FRAGILITY INNER ASPECT OF ARM
4	121,600	4'15"	5'30"	17.5	19.0
5	148,000	3'30"	5'00"	20.4	21.2
6	182,000	3'15"	5'00"	22.7	24.0
7	174,000	3'30"	4'45"	24.5	25.1
8	200,000	3'00"	4'30"	26.0	26.0

Only one-half of these patients had exhibited fever of any degree and all of them recovered. The result of an examination of them for evidence of a hemorrhagic tendency is shown in Table 34. In comparison with Table 33, it can be seen that the bleeding time and the platelet counts show the greatest difference; and that in this particular series all the average values for bleeding time and clotting time are within the limits of normal. None of these patients had clinical evidence of purpura. In November, i.e., later than 15 weeks after the bombing, the bleeding time and clotting time (capillary tube method) of 30 patients convalescent from radiation injury and other injuries was measured at the Omura Naval Hospital. All the results were normal, and the longest bleeding time observed was 4'30". The longest clotting time was 3'15". These patients were all members of the group cited in a previous section. The average platelet count for this class of patient at Omura was 176,000.

SUMMARY

1. In the severe cases, the hemorrhagic state was a common finding, which was probably declining in frequency and severity after the 7th-8th week after irradiation.

2. It appears from the material that has been presented that in the moderately severe and mild cases there was little evidence of a serious hemorrhagic tendency.

3. On the basis of the laboratory report submitted by the Japanese it is seen that the hemorrhagic state in patients with the syndrome of radiation injury closely resembled the so-called "toxic", or secondary thrombocytopenic purpura.

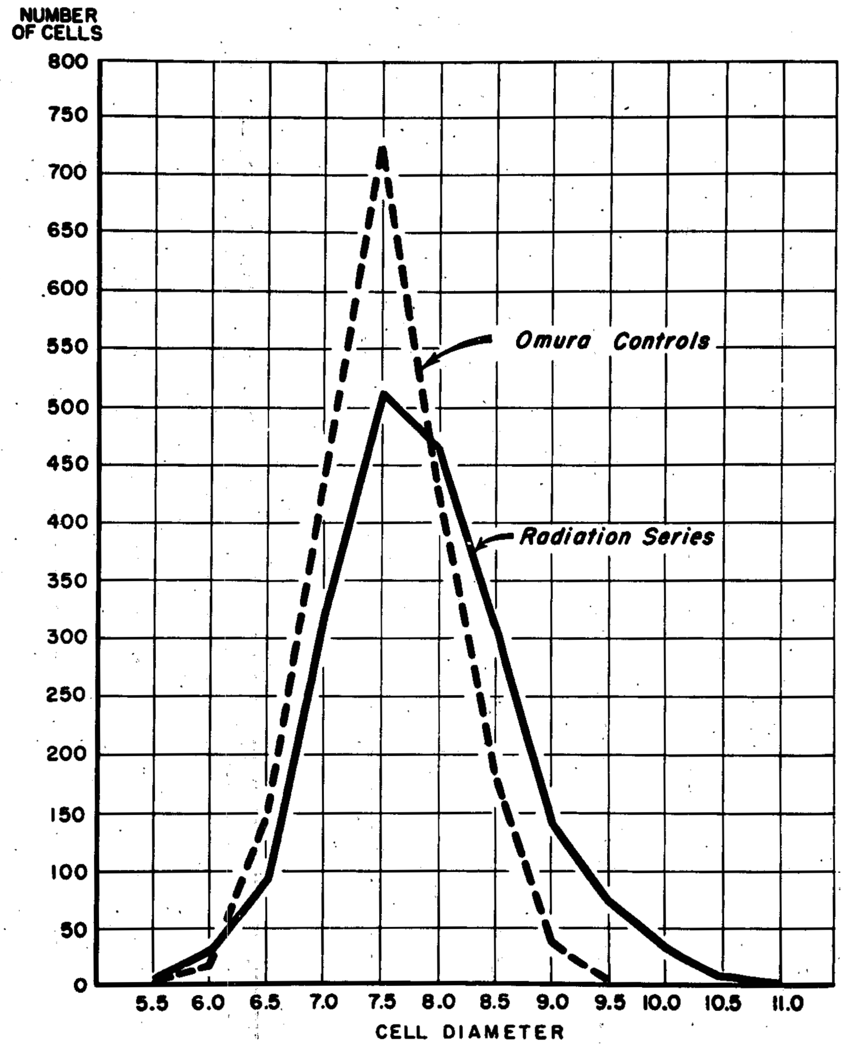


Fig. 1 (6)--Price-Jones' curves for normal control subjects from Omura City; and for 20 patients with radiation sickness. See Figure 2 (6). (Photo File # NM 101.)

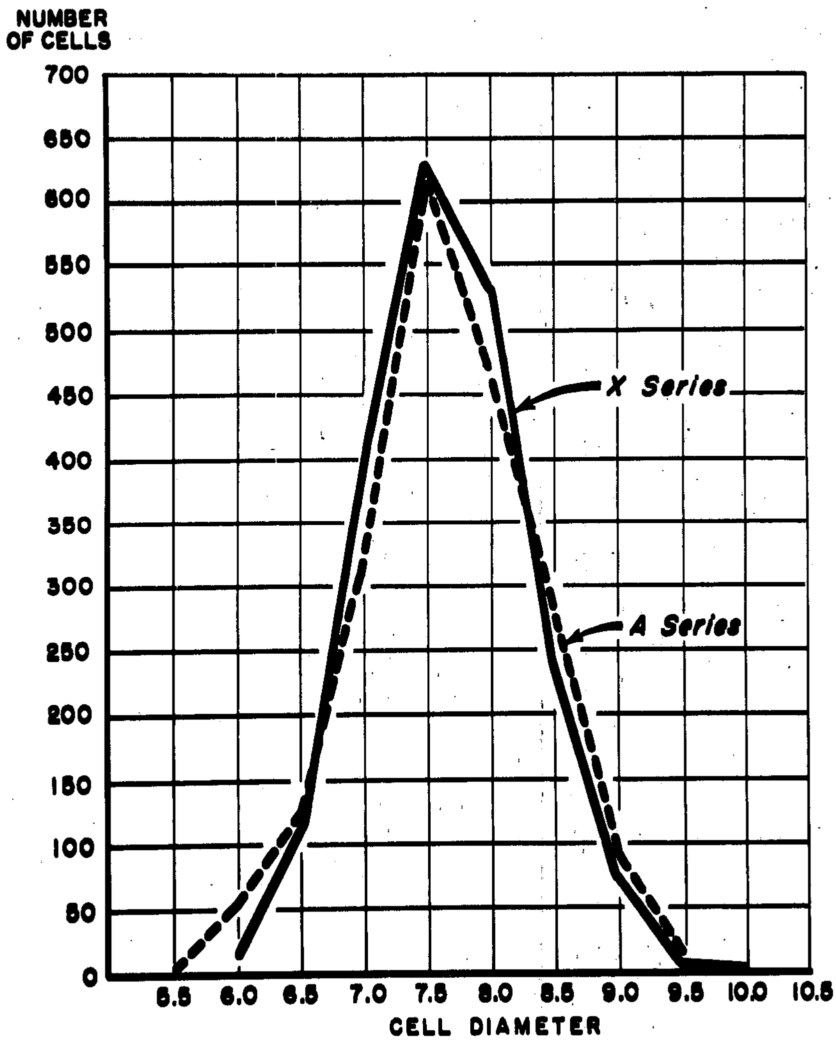


Fig. 2 (6)--Price-Jones' curves for two groups of residents of Nagasaki: Series A had no clinical evidence of radiation disease. Series X were in a part of the city completely shielded from the gamma rays by the hills. (Photo File # NM 102.)

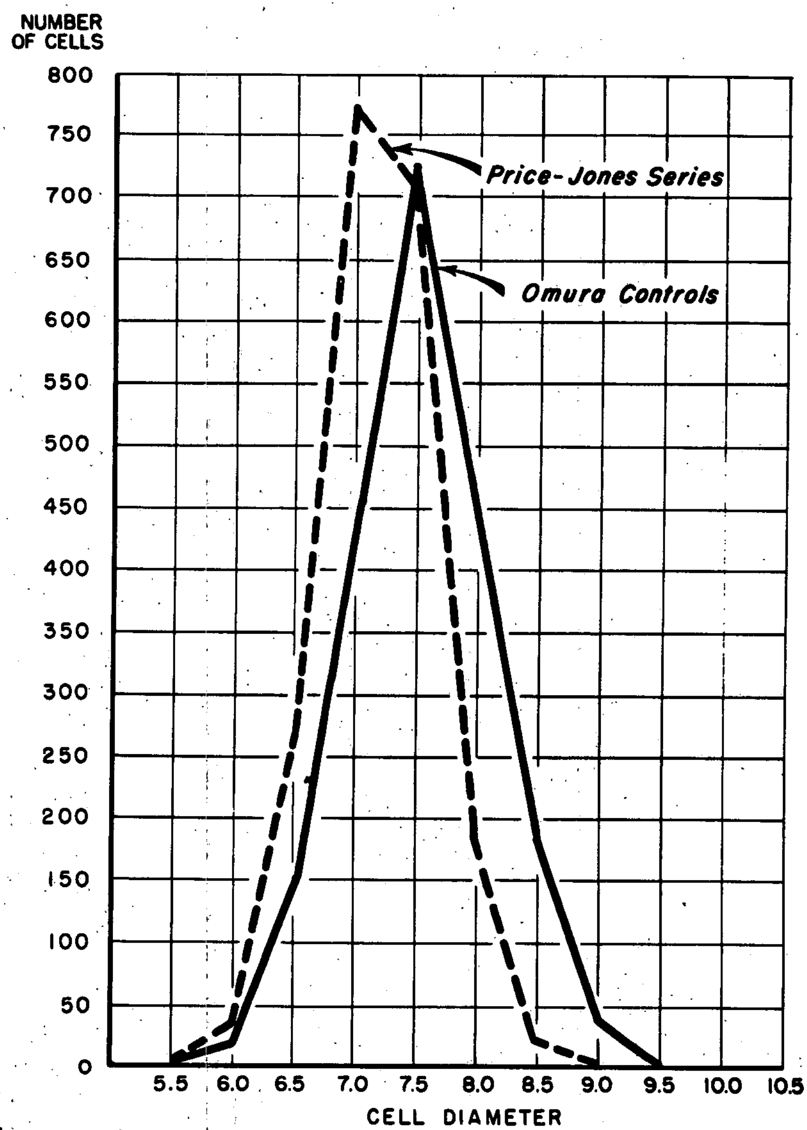


Fig. 3 (6)--Comparison of Price-Jones' original normal curves, and the normal control subjects from Omura City. (Photo File # NM 100.)

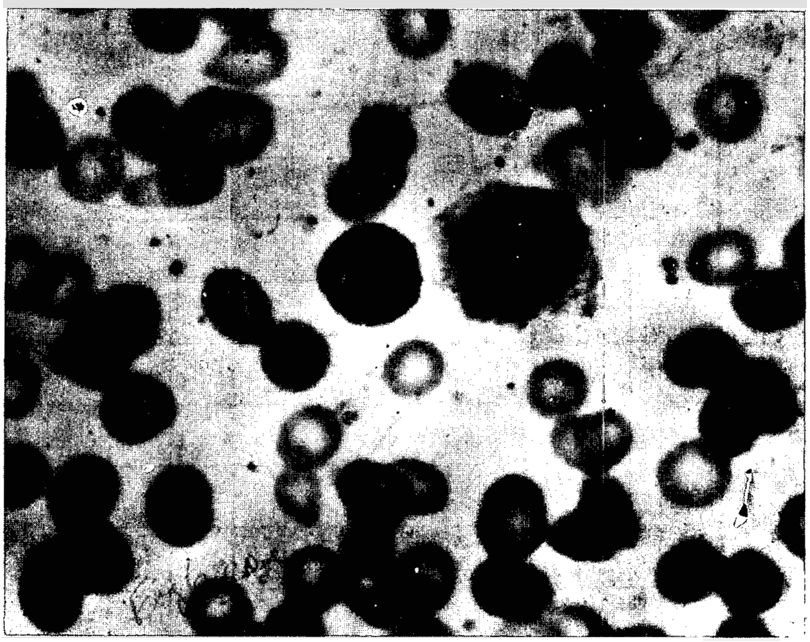


Fig. 4 (6)--Dohi, 20. Female. 1100 meters. Blood film, 25 October 1945, showing basophilic stippling of erythrocytes, and an abnormal lymphocyte. X 1200. Omura Naval Hospital, Case # 3058. (Photo File # HM 133K.)

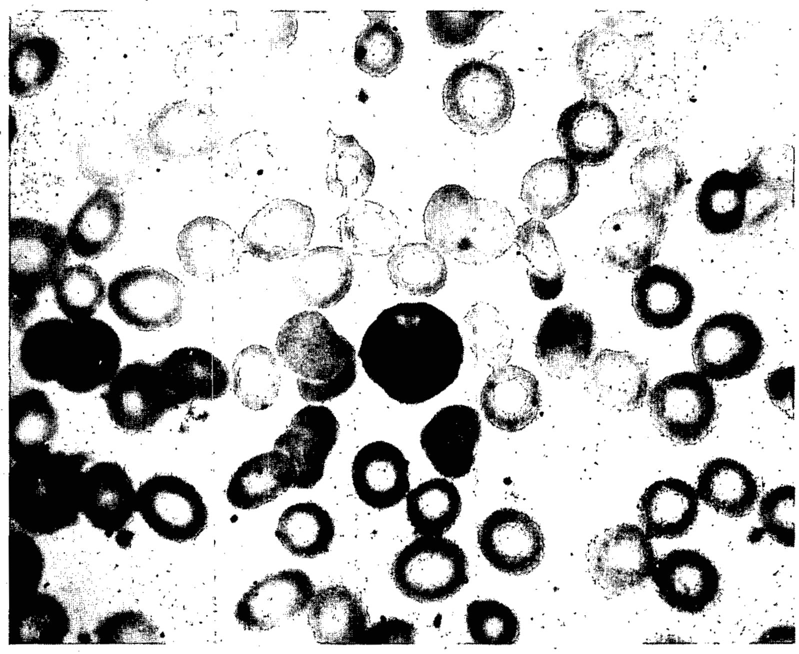


Fig. 5 (6)--Dohi, 20. Female. 1100 meters. Blood film, 25 October 1945, showing abnormal lymphocyte X. 200. Omura Naval Hospital Case No. 3058. (Photo File # NM 139K.)

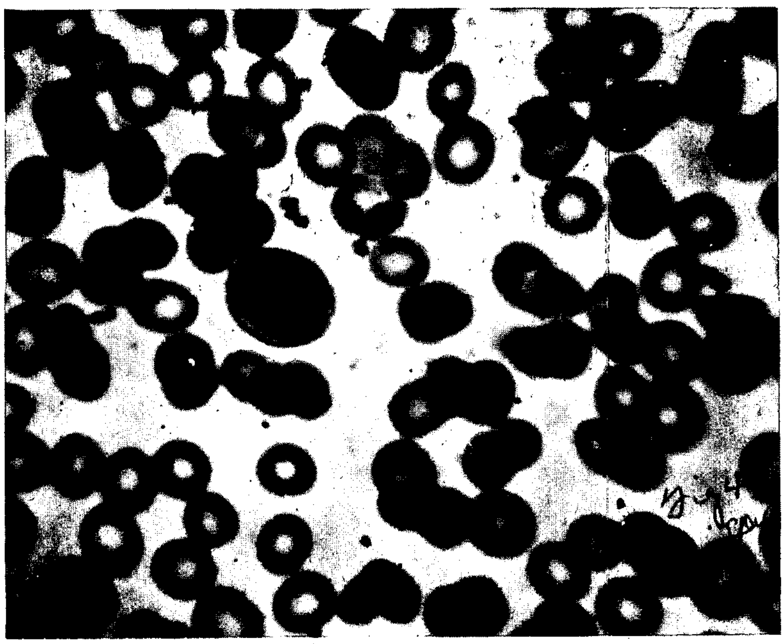


Fig. 6 (6)--Tuzino, 17. Male. 1100 meters. Blood film, 26 October 1945, showing histiocyte (reticulum cell) and abnormal lymphocyte. X 1200. Omura Naval Hospital Case No. 3058. (Photo File # NM 140K.)

Section 7

STUDIES ON BONE MARROW OBTAINED BY BIOPSY

Prepared by George V. LeRoy, Lt. Col., MC

Data Collected by George V. LeRoy, Lt. Col., MC, Averill A. Liebow, Lt. Col., MC, Samuel Berg, Major, MC, K. Nakao, MD, K. Kishimoto, MD.

B.
General.

The examination of specimens of bone marrow obtained by biopsy is a well established practice in the study of diseases of the hematopoietic system. The technique of sternal puncture is simple and comparatively painless, and is seldom followed by serious complications. In the case of patients suffering from the effects of large amounts of gamma radiation, biopsy of bone marrow yielded material which could be used by the clinicians to determine:

a) The nature and extent of the injury to the bone marrow; and

b) The stage and the degree of regeneration of the hematopoietic functions.

A combined study of bone marrow obtained at biopsy and at autopsy has made possible a careful cytologic investigation of the manner in which the human tissue reacts after destruction of the definitive cells by gamma rays. The large number of specimens obtained in Japan has afforded a unique opportunity to study these fundamental vital processes on a broader scale than has ever been possible with human material, or ever attempted with lower animals. The general effect of gamma rays on bone marrow is well known: sufficiently large amounts destroy a part or all of the definitive cells. The consequences of this are reflected in the blood by the development of granulopenia and anemia. Since the lymphopoietic tissues are also destroyed by such doses of radiation delivered to the whole body, extreme leukopenia occurs.

In the case of human subjects, the scientific literature contained no precise information on the following:

a) The amount of ionizing radiation required to destroy all the definitive elements of the marrow, and of the lymphatic tissues.

b) The amount of ionizing radiation required to destroy not only the definitive elements, but also the mesenchymal, or reticulo-endothelial elements.

c) The rate at which definitive cells disappear from the bone marrow, the lymph nodes and the blood after amounts of ionizing radiation, as in (a); and as in (b).

d) The rate at which regeneration of any of these definitive elements proceeds after a dose of ionizing radiation of such magnitude that it can occur.

e) The manner in which a new marrow develops to replace the tissue destroyed by ionizing radiation.

In the following discussion of the bone marrow, certain points of view will be adhered to; and it is well to present them at this time:

a) It is assumed, and with good reason, that there is a close parallel between the bone marrow obtained by biopsy and that obtained at autopsy in a comparable stage of the reaction after irradiation. In the preparation of this section both types of material were studied, and the conclusions that are offered are based on the combined study. The autopsy specimens, however, are described in the section on pathology (See Section 8) because it seemed unreasonable to divorce the hematopoietic system from the remainder of the tissues. In the present section, the attempt will be made to discuss the marrow in a manner which will aid clinicians in understanding the changes which occurred.

b) It is assumed that the specimen of marrow obtained by biopsy from a given case is reasonably representative of that tissue as a whole. It well recognized that this is not always true; and it is possible that discrepancies were greater than usual in the victims of the atomic bomb. Nevertheless, the amount of material available is so large, and the responses are so consistent that no useful purpose is served by equivocation of this sort.

c) There should be no question of the propriety of a joint discussion of specimens from Hiroshima and Hagasaki. Although the fissionable material in the two bombs was different, there is no reason to think that the type of gamma radiation varied significantly in quality. The effective range for gamma ray injury was not materially different in the two cities. In any case, the discussion which follows this is not important because the major emphasis will be on the type of reaction rather than the quantity of ionizing radiation responsible for it.

Material.

The following material was available for examination:

Hiroshima

Bone marrow biopsies.......178

Serial biopsies............ 24

Bone marrow from autopsies. 32 (approximately)

In spite of the fact that the Japanese were aware of the fact that gamma rays were emitted by the exploding bombs, and in spite of their early recognition of the syndrome of radiation injury, few specimens of marrow were obtained during the first three weeks after the bombing. There are several reasons for this:

a) The attending physicians were too busy to perform biopsies, and the value of the marrow from autopsies was not fully appreciated.

b) During the first few weeks most of the doctors were Army or

Navy surgeons and proper specimens were not obtained until the research teams from the Medical Schools arrived.

c) The military surgeons were less congenial to the American doctors than the University faculty members. The latter were much more generous with their specimens and preparations.

Whatever the reasons were, it is regrettable that the material from the early cases, i.e., the ones whose sickness and death occurred in August is relatively scarce. From such cases, the following specimens of marrow are available:

Hiroshima	Biopsy	2
	Autopsy	7
Nagasaki	Biopsy	0
	Autopsy	0

Technical Methods.

The specimens of bone marrow were obtained in most instances by sternal puncture and in a few instances by puncture of the spinous process of a vertebra. The Japanese doctors used a variety of needles and trephine needles, but in general seemed to prefer the simplest arrangement. One physician, Dr. MASUYA of Kyushu Imperial University, obtained marrow from fresh cadavers using a carpenter's gimlet and a small needle and syringe. The amount of marrow that was aspirated was usually small, and the slide preparations were quite satisfactory as a rule. In some clinics the number of erythrocytes and nucleated cells was counted, but this was not done generally. These slides were fixed with methanol and stained with dilute Giemsa stain. The biopsies that were performed by members of the Joint Commission were done in a similar manner, with the exception that Wright's stain was used, and then the film was counter-stained with Giemsa.

NOMENCLATURE

The science of hematology is complicated by the various systems of nomenclature that have been introduced. In discussions with the Japanese doctors, an effort was made to determine which system they employed so that their reports and clinical records of early cases could be interpreted properly. For the discussion that follows it is desirable to present the nomenclature which will be employed; and in the case of the cell with diverse names, the cytological description of it.

(1) Definitive blood cells: This term is applied to all stages of the types of cells that are found in normal blood. It is used specifically for all the members of the granulocytic series, the erythrocytic series (excepting the megaloblasts); the large, medium-sized and small lymphocytes and the normal lymphoblasts; the megakaryocytes and platelets; and the ordinary monocytes.

(2) Reticulum: This term is used in a general sense to include reticulo-endothelial cells of any type, macrophages, histiocytes, clasmatocytes, etc. In a narrow sense it is used to refer to the elongated stellate cell with non-granular faintly basophilic ground-glass type of cytoplasm, with an oval, vesicular nucleus and small, inconspicuous nucleoli which appeared in large numbers among the fat cells, and between the fat cells and sinusoids, and within the sinusoids of the marrow. Rounded, free forms of this same general type were also designated reticulum cells.

(3) Reticular elements: This term is used in a general sense to designate the various types of reticulum cell (as in 2 above) as well as a variety of mononuclear cells apparently derived from, or at least existing in close proximity to the reticulum.

(4) 'Blasts: This term is used for cells with the following characteristics: The cytoplasm is homogeneous, nongranular, comparatively scanty and basophilic. The nucleus is generally rounded, but no significance is attached to variations in shape so long as the chromatin threads are of fine quality and closely packed. The nuclear membrane is thin. Nucleoli are considered a prerequisite for the diagnosis of 'blast. No significance is attributed to the number or shape of the nucleoli. No effort is made to distinguish "myeloblasts" from "lymphoblasts" or from "monoblasts". The use of special names for immature types of 'blast has been avoided. A regular series of stages intermediate between the typical 'blast of normal marrow and rounded "free" reticulum cells was encountered. The cell is designated as 'blast or reticulum cell, depending on which characteristics preponderated.

(5) Promyelocyte: This term is applied to cells with the general specifications of the 'blast (as in 4 above) which have non-specific azurophile granules in the cytoplasm.

(6) Myelocyte: This term is applied to cells which contain the specific type of granulation: neutrophilic, eosinophilic or basophilic as well as the nonspecific azurophile granules. In practice it is convenient to consider that granules which are seen overlying the nucleus are of the non-specific type. The nucleus of such cells is generally more mature with coarse bands of deeply staining chromatin and prominent nuclear membranes.

(7) Metamyelocyte: This term is applied to cells which contain only the specific granulation. Indentation of the nucleus is considered a desirable, but not a necessary characteristic.

(8) Stab forms and Poly: These terms are applied to the nonsegmented and segmented mature granulocyte, respectively.

(9) Lymphocytes: The characteristic small, medium-sized, and large lymphocytes that are seen in normal blood films should not cause any special difficulty in identification. There is little likelihood of confusion in respect to these terms.

(10) Abnormal Lymphocytes: This term is applied to a series of mononuclear cells of quite distinctive appearance. The cells are of various sizes, some as small as 10-15 microns, others as large as 35-40 microns. The cytoplasm is abundant and homogeneous and contains either no granules or small azurophilic ones. In some instances the cytoplasm is clear and glassy with only a faint tinge of basophilia, which tends to accumulate as the periphery of the cell. In others, the cytoplasm is more basophilic, flocculent, or of a ground-glass appearance. Vacuoles are infrequent, except in cells with very marked basophilia (as the Türek-type cell). The nucleus of the abnormal lymphocyte is also variable in appearance, but there appears to occur a definite series of types. It is usually round, and excentrically located. At one extreme the chromatin occurs in rather large clumps or threads, and there is so little contrast between chromatin and parachromatin that the nucleus appears homogeneous. At the other extreme the nucleus is vesicular, and the chromatin occurs in a fine meshwork, and there is somewhat more contrast with the parachromatin. Nucleoli are small and inconspicuous, and the nuclear membrane is fine. Many of the cells to which this designation is applied are identical in appearance with the familiar "atypical lymphocyte" of infectious mononucleosis. The diversity of forms is even greater, however, in the material from the patients exposed to gamma radiation. In some instances (see below) there is no doubt but that typical specific myeloid granulation developed in the cytoplasm of the "abnormal lymphocyte." When this type of cell is encountered, it is designated

a "myelocyte."

(11) Plasma cells: This term is used in the conventional manner for a whole series of mononuclear cells varying in size from 10 to 30 microns. The cytoplasm is non-granular, homogeneous and strongly basophilic, and contains a pale region or a vacuole adjacent to the nucleus. The nucleus is always round and contains coarse bands of dark staining chromatin, often arranged radially, which contrasts sharply with the very pale parachromatin. In the going forms, one or two small pale nucleoli are seen. The nuclear membrane is indistinct, and the cells frequently contain two or more nuclei. In general, any cell which resembles the varieties of mononuclears to be seen in multiple myeloma is called a plasma cell.

(12) Monocytes. This term is used in a conventional sense to describe large mononuclear cells with abundant pale, basophilic, lavender, cytoplasm containing a variable number of fine azurophile granules. The nucleus is often indented, or lobulated, and typically has a folded appearance. The chromatin occurs in moderately fine interlacing threads, relatively widely spaced with dark nucleolus-like accumulations. The cytoplasm of monocytes in bone marrow frequently contains vacuoles. These cells often presented great difficulty in identification, and the use of the term was restricted to very typical examples

(13) Histiocyte: This term is applied to large cells with abundant finely granular, palely basophilic, ground-glass type cytoplasm. Phagocyted pigmented particles and cellular debris is seen in many. The nucleus is oval, vesicular, with a fine nuclear membrane and a few small nucleoli. The presence of phagocytosed material in a large cell always justified the designation of histiocyte. Obviously similar cells, but without phagocytosis are similarly labelled. These cells are called macrophages, alternatively. In the differential counts all the reticular elements recognizable as such are included in

the category of histiocytes. In the discussion that follows, histiocytes are frequently grouped with "reticulum cells".

(14) Nucleated red cells. The decision was made early in the study to classify the nucleated red cells in a simple manner. Accordingly, they are differentiated only on the basis of whether they contain hemoglobin: normoblasts; or do not contain hemoglobin: erythroblasts. It was decided to distinguish megaloblasts, if found, in this manner: Very large cells with abundant, densely basophilic, nongranular cytoplasm; the nucleus is round, relatively small in proportion to the cytoplasm, has an indistinct nuclear membrane, a rather vesicular nucleus with lacy chromatin, and inconspicuous, large, irregular nucleoli. The type cell is that seen in pernicious anemia in relapse, and it was thought that typically there should be a series of more mature hemoglobin-containing forms with the characteristic nucleus. Large basophilic nucleated red cells were seen in abundance in the Japanese material; but in no case were all the criteria for the designation of megaloblast satisfied. It seems likely that in these preparations, the majority of cells so named would be called "pro-erythroblasts" or "pronormoblasts" by most hematologists.

The most immature stages of the erythroblast are difficult or impossible to differentiate from 'blasts. In most instances, however, the basis for identification as a nucleated red cell (erythroblast) is the greater density of the basophilic cytoplasm, the coarse quality of the nucleus, the more distinct nuclear membrane, and the smaller, indistinct nuclei.

(15) Megakaryocytes: The term is used in a conventional manner and the identification is not difficult in smear preparations. In tissues, however, multinucleoated reticulum cells frequently make interpretation a problem.

Normal Values.

The average values for differential cell counts of sternal marrow obtained from normal Japanese subjects is presented in Table 1. Similar values for Occidentals are offered for comparison:

TABLE 1

	JAPANESE		OCCIDENTAL
AUTHORITY	KOMIYA*	MISAO*	WINTROBE***
Myeloblast	1.8	1.4	2.0
Promyelocyte	3.8	10.9	5.0
Neutrophil myelocyte	5.1	8.7	12.0
Neutrophil metamyelocyte	7.8	12.0	) 22.0
Neutrophil stab form	16.6	15.0	)
Neutrophil polymorphonuclear	20.2	11.9	20.0
Eosinophil (all stages)	4.2	4.3	3.5
Basophil	0.3	--	0.5
Lymphocyte	16.8	17.3	10.0
Monocyte	3.1	0.8	2.0
Histiocyte	1.0	0.2	0.2
Plasma Cell	-	1.1	0.4
Erythroblast	3.0	6.1	4.0
Normoblast	16.0	10.0	18.0
Total Nucleated Cells	100,000	100,000-150,000	100,000
Myeloid:Erythroid Ratio	3:1	4:1	3:1

*Komiya-Text book of Hematology, published in Japan.

**Misao, T.-See appendix , Reference . This is a useful group. The study was made in 1945 of 28 normals, for comparison with the findings in the patients with radiation injury.

***Wintrobe, M.M. "Clinical Hematology," Philadelphia, Lea & Febiger, 1942, Page 44.

Classification of the material: date of biopsy.

In a general review of the biopsy material it was found that it could be grouped conveniently on the basis of the time of collection. This distribution is shown in Table 2.

TABLE 2

HIROSHIMA	DATE	NAGASAKI
6 August	Date of bombing	9 August
2	During August	0
33	1-14 September	42
11	15-30 September	6
19	October	91
15	November	24
0	December	15
80	Total	178

Type of Patient.

With a very few exceptions, biopsy of sternal marrow was only performed on patients with frank clinical evidence of radiation injury, or on those in whom it was a reasonable possibility. For that reason it is to be expected that they were close to the center of the explosion. The distribution of the patients in relation to their approximate distance from the bomb is shown in Table 3.

Total Nucleated Cell Counts.

Counts of the nucleated cells in the bone marrow obtained by aspiration biopsy were not made in every case. A sufficient number of representative ones are available, however, to illustrate the trend of this value in patients with several radiation injuries. (See Table 5). The normal value for Japanese is 100,000 to 150,000 per cubic millimeter.

TABLE 3

HIROSHIMA PATIENTS	DISTANCE FROM BOMB, METERS	NAGASAKI PATIENTS
9	0-500	6
36	600-1000	23
20	1100-1500	57
2	1600-2000	21
2	2100-2500	9
0	2600-3000	4
0	Not stated	34
69	Total	154

The diagnoses which appeared in the clinical records of the patients studied are listed in Table 4.

TABLE 4

HIROSHIMA		DIAGNOSIS*	NAGASAKI	
62	88%	Radiation injury	128	99%
11	16%	Burns	65	50%
45	64%	Wounds	56	43%
8		Not stated	13	

*The number of diagnoses adds up to more than the number of cases (See Table 3) because many patients had more than one injury. The percentage (table 4) are calculated on the basis of 129 patients for Nagasaki; and 71 for Hiroshima.

TABLE 5

TOTAL NUCLEATED MARROW CELL COUNTS

HIROSHIMA			NAGASAKI	
AVERAGE	NUMBER OF CASES	TIME OF EXAMINATION	NUMBER OF CASES	AVERAGE
11,000	25	1-14 September Range for Hiroshima: 1100 - 62,000 Range for Nagasaki: 800 - 40,900	48	20,600
90,000	14	1-31 October Range for Hiroshima 21,00 - 250,000 Range for Nagasaki: 60,00 - 270,000	11	168,000
81,000	7	1-31 November Range for Hiroshima 29,500 - 150,000		
		1-17 December Range for Nagasaki 16,400 - 120,000	15	60,000

DIFFERENTIAL COUNTS OF BONE MARROW: GENERAL

It is customary to report the result of examination of bone marrow biopsy material in terms of a differential count of 200-500 cells. The preparations from the victims of the atomic bomb were all studied and counted by the same person to insure consistency in the interpretation and recording of the counts. Ideally, it would be desirable with such large numbers of cases, after calculating mean values for each type of cell, to treat the data statistically in order to demonstrate the deviations from normal. Unfortunately, such treatment of marrow differential counts is not very satisfactory because of the wide variation in the distribution of individual cell types. This factor is illustrated in Table 6 where the means, standard deviations, and range of normal variability for each cell type in normal marrow are shown. It is apparent from the tabulation that small or subtle changes in the differential count of marrow obtained by puncture biopsy need not be anticipated, and cannot be proved satisfactorily. In spite of this qualification, it is desirable to present the results of the counts in appropriate groups, with mean values for the various elements to facilitate comparisons.

The Type of Injury.

Throughout the entire study of the marrow, the focus of interest was on the nature of the changes attributable to ionizing radiation. Because of this, patients were selected for biopsy because they presented symptoms of radiation injury, or because it was suspected to have occurred. Many of the subjects, however, had sustained other injuries, or had acquired complicating infections, or suffered from malnutrition. Any or all of these factors

TABLE 6

STATISTICAL DATA - 52 HEALTHY MALES*
All values in per cent

CELL TYPE	MEAN	STANDARD DEVIATION	RANGE OF VALUES **	
Myeloblast	1.3	0.6	0	3.0
Promyelocyte	1.4	0.8	0	3.6
Myelocyte	15.0	3.8	3.7	26.3
Metamyelocyte	15.7	3.2	6.0	25.4
Stab Form	10.5	3.7	0	21.7
Polymorphonuclear	20.9	5.5	4.5	37.3
Lymphocyte	16.8	4.8	2.5	31.1
Monocyte	1.7	0.6	0	4.9
Plasma Cells	0.4	0.3	0	1.4
Histiocyte	0.3	0.1	0	0.25
Nucleated Red Cells	12.9	4.4	0	26.1

*Segerdahl, E., "Ueber Sternalpunktionen"
Acta Medica Scandinavica, 1935, Sppl. 64.

**Mean plus or minus three standard deviations is generally accepted as the limits of normal variability.

are theoretically capable of provoking reactions in the marrow which might alter the pattern of injury or regeneration induced by the gamma rays. Actually, no such effect was found when several groups of patients who were biopsied at similar times were compared. A typical sample of the type of result from this study is shown in Table 7. On the basis of this analysis it seems justifiable to consider all the patients together and to form groups for comparison on the basis of the time at which they were studied.

The Time Realtionship.

The examination of the autopsy material has shown that regeneration of some sort can be seen in nearly every specimen obtained from patients who survived longer than approximately 7 days after the bombing. This observation is in agreement with comparable animal experiments. Because of this fact, it is important to bear in mind that the bone marrow obtained by biopsy represented samples from regenerating marrow. It is desirable, therefore, to study the tempo as well as the nature of the regenerative process. Unfortunately, these considerations were not completely apparent to the Japanese physicians who performed the biopsies on the early cases, and for this reason, specimens were not always obtained at the most propitious times. The trend of the process of regeneration is best demonstrated in the material from Nagasaki. Average values for the differential marrow cell count during certain intervals after 9 August are presented in Table 8. The fate of the individual patients, particularly in the time-period 1-14 September, is not known in every instance, so that it is necessary to include here the ones that died with the survivors. Regardless of this fact, there is a definite progession of changes in the percentage of each cell type as recovery proceeds. When these mean values are considered in relation to the total count of nucleated cells, it is

TABLE 7

EFFECT OF OTHER INJURIES ON MARROW CHANGES DUE TO GAMMA RADIATION. (NAGASAKI)

	DATE EXAMINED						
	1-14 September			16-31 October			
TYPE OF CELL	R *	RBW	TYPE OF PATIENT	R	RB	RW	RBW
Blast	3.0	5.1		0.7	0.8	0.9	2.1
Promyelocyte	5.3	5.0		4.8	1.8	2.1	2.5
N. Myelocyte	4.7	0.9		12.7	8.0	7.6	8.1
N. Metamyelocyte	4.7	2.4		12.5	11.4	13.7	11.4
N. Stab	6.0	4.0		18.5	21.3	19.1	19.2
N. Poly	3.9	3.5		10.5	12.4	13.9	9.2
Eosinophil (all)	2.1	3.0		3.1	4.6	7.2	7.5
Lymphocyte	37.6	48.7		7.4	5.1	8.2	6.6
Monocyte	1.3	0.4		1.4	0.9	2.0	1.1
Histiocyte	9.2	10.5		0.1	0.4	0.4	0.2
Plasma Cell	11.8	8.2		1.1	0.8	1.3	1.3
Erythroblast	1.6	0.9		4.6	9.4	4.6	5.1
Normoblast	8.8	7.4		22.6	23.1	19.0	25.7
Number of Cases	32	10		12	25	20	10

*R: Radiation injury only.

RB: Radiation injury plus burns

RW: Radiation injury plus wounds

RBW: Radiation injury plus burns plus wounds.

TABLE 8

NAGASAKI

AVERAGE DIFFERENTIAL COUNTS OF STERNAL MARROW

	DATE					
CELL TYPE	1-14 Sept.	15-30 Sept.	1-15 Oct.	16-31 Oct.	Nov.	Dec.
Blast	3.5	2.8	1.2	1.0	1.0	1.0
Promyelocyte	5.2	3.9	3.1	2.5	2.0	0.7
N.Myelocyte	3.8	10.2	11.6	8.7	6.1	3.0
N.Metamyelocyte	4.2	12.6	11.3	12.3	11.8	11.0
N.Stab form	5.5	18.7	19.8	19.9	23.6	24.0
N. Polys	3.8	12.3	15.4	12.0	15.1	15.8
Eosinophil (all)	2.3	2.1	5.5	5.5	4.9	6.5
Lymphocyte	40.2	16.4	5.6	6.7	9.9	16.4
Monocyte	1.1	2.3	1.0	1.3	2.0	4.4
Histiocyte	9.5	1.5	0.5	0.3	0.4	1.2
Plasma Cell	11.0	3.4	1.3	1.1	1.7	1.1
Erythroblast	1.4	0.3	5.9	6.5	3.5	1.7
Normoblast	8.5	15.4	17.8	22.2	18.0	13.2
Number of cases	42	6	24	67	24	15

Total Nucleated
Cells (from table 5) 20,600 168,000 60,000

possible to visualize in a general way the rate of regeneration of the different definitive elements of the marrow. In the course of study of the material it was found that it was very convenient to consider the marrow cells in four broad groups:

1) Myeloid-All the members of the granulocytic series.

2) Lymphoid-The small, medium-sized, large, and abnormal lymphocytes.

3) Reticular-The plasma cells, monocytes, histiocytes, and all other frankly reticular elements.

4) Erythroid-The erythroblasts and normoblasts.

This type of grouping, in addition to permitting an easier comprehension of the general pattern of divergence from normal, can also be used to calculate the Myeloid:erythroid ratio. This ratio is a useful expression to indicate the relative extent of activity of each of these two vital systems. Using the simplified means of presentation, the averages of all the differential counts for each city, are listed in Table 9 and are shown graphically in figures 1 and 2. It will be seen in Table 9 in the time period: 1-14 September, for the Hiroshim patients, that there is a division of the average values on the basis of whether the patient lived or died. The difference is striking. Unfortunately, the records do not permit such a division of the data from Nagasaki, but there is no good reason for thinking that the results would not be similar. It should also be noted that in the "pie" diagram of Figure 2, all the differential counts for the two periods 15-30 September, and 1-15 October, are grouped together. This is quite proper since a consideration of the individual counts in each group showed that the similarities were striking; and that the excessive erythopoiesis of the time period: 16-31 October, was seldom in evidence earlier. (See table 8)

From a study of the averages of the differential cell counts of bone

TABLE 9

CONDENSED DIFFERENTIAL COUNTS AT DIFFERENT TIME PERIODS

HIROSHIMA					TIME PERIOD	NAGASAKI				
M*	L	R	E	M:E RATIO		M:E RATIO	M	L	R	E
36.1	28.6	22.1	13.4	2.7:1	1-14 Sept. All Pts.	3.0:1	28.3	40.2	21.6	9.9
18.3	39.6	36.3	5.9	3.2:1	Pts. who died	-	-	-	-	-
59.3	15.8	8.0	16.9	3.5:1	Pts. who survived	-	-	-	-	-
62.4	8.7	4.7	24.2	2.6:1	15-30 Sept.	3.8:1	60.7	16.4	7.2	15.7
61.0	15.1	3.7	20.2	3.0:1	1-15 Oct.	2.9:1	67.9	5.6	2.8	23.7
46.3	24.2	4.7	24.8	1.9:1	16-31 Oct.	2.2:1	61.9	6.7	2.7	28.7
58.9	18.2	3.9	19.0	3.1:1	November	3.0:1	64.5	9.9	4.1	21.5
-	-	-	-	-	December	3.5:1	62.0	16.4	6.7	14.9
64.5	17.3	2.1	16.1	4.0:1	Normal A**	4.0:1	64.5	17.3	2.1	16.1
60.1	16.8	4.1	19.0	3.2:1	Normal B***	3.2:1	60.1	16.8	4.1	19.0

*M: Myeloid; L: Lymphoid
R: Reticular; E: Erythroid

**Misao. See table 1.
***Komiya. See table 1.

marrow, certain general principles can be recognized which will not only aid in understanding the reaction as a whole, but also help in the interpretation of the findings in individual cases. These general principles are as follows:

1) Regardless of the ultimate outcome in individual cases, the group of patients that survived and were biopsied in the period: 1-14 September, or $3\frac{1}{2}$ to 6 weeks after the bombing, showed some evidence of myelopoiesis and erythropoiesis. Judging from the myeloid: erythroid ration the relative amount of regeneration was approximately equal in each system.

2) When the differential counts were classified on the basis of whether the patient survived or died, there was a striking difference in the percentages of myeloid and erythroid cells of each group. In the case of the former, the values were 59.3% and 18.3% for surviving and fatal cases, respectively. In the case of the erythroid series, the values were 16.9% and 5.9% respectively. It is known from a study of the autopsy specimens that proliferation of the reticulum in the bone marrow occurred in virtually every patient who survived longer than 7-10 days after exposure to the gamma radiation. It is also known from the pathological material that at some time in the period: 7-21 days after the bombing, the first evidence of myelopoiesis and erythropoiesis was found. Putting all these observations together leads to the conclusion that the extent and the rapidity of the metamorphosis of proliferating reticulum in the marrow into myelopoietic and erythropoietic tissue are critical factors for survival.

3) In the first group of Nagasaki patients studied in the time period: 1-14 September there was a marked shift to the left of the granulopoietic system. This can be expressed quite readily by the ratio 'Blasts: Polys, which was 90% at this stage. In the next period: 15-30 September, the ratio was 25%

and after 1 October, the ratio was normal, or less than 10%. This observation can be interpreted to indicate that on the average, myelopoiesis achieved an approximately normal pattern about 7-8 weeks after exposure to the gamma radiation emitted by the atomic bomb. This finding is especially interesting because it has already been shown (see table 5) that the highest values for total nucleated marrow cell counts occurred in the period: 7-12 weeks (i.e. during October) after the bombing.

4) In the material from each city, the maximum intensity of erythropoiesis occurred in the period: 16-31 October, or 10-12 weeks after the bombing. The evidence for this observation is the myeloid: erythroid ratios, which were 1:9:1 and 2.2:1 for Hiroshima and Nagasaki material respectively in that time period. These were the lowest values for the M:E ratio that were seen in any period. They are especially significant because the highest total nucleated marrow cell counts were found during October. In Biopsies obtained in November (i.e. later than 12 weeks after the bombing_) the ratios were normal in each series. The average values found were 3.1:1 for Hiroshima, and 3.0:1 for Nagasaki.

5) The only marked difference between the average differential count of marrow cells in the material from the two cities was found in the percentage of lymphocytes in the specimens collected during October and November. There does not appear to be any simple explanation for this finding.

6) In the tabulation of the average differential counts the megakaryocytes have been omitted. This was done because of the great variation in the percentages found. In general, it may be said that the megokaryocytes and the blood platelets returned to the marrow and the circulating blood at the same rate as the granular leukocytes. The behavior of these elements is described

in the sections on Blood. (Section 6) and in that on Pathology (Section 8).

7) In general, it appeared that the average bone marrow, as judged by the differential cell counts, had returned to normal in November, 1945, or 12-16 weeks after injury by the ionizing radiation of the atomic bomb.

ILLUSTRATIVE CASES

One of the most interesting features of the specimens of bone marrow was the remarkable diversity of the material obtained from patients early in the course of the syndrome of radiation injury. This was due in part to the fact that the appearance of rapidly regenerating marrow changes almost from day to day, and certainly from week to week. Since the majority of the biopsies were not made according to any schedule or plan, it was not surprising that these differences would be great. Even when the examination was not performed at random, it was usually found that samples obtained from patients in apparently identical stages of recovery after equal exposure to radiation would be entirely different. It was apparent from these observations that the recovery process could occur not only at varying speeds, but also in varying ways. Before describing the cytologic details of the regeneration, it is appropriate to present some specific examples of patients who recovered, and on whom serial bone marrow biopsies were performed. It is important from the clinical standpoint to discuss the reaction of the marrow to radiation injury, with particular regard for the possibility and the mechanism of recovery.

As a preliminary to the presentation of the records of survivors, it is desirable to consider three patients who died with typical symptoms of severe radiation injury a few days after biopsy of the sternal marrow was performed. All three patients were in Nagasaki. Two were in brick buildings at 500 meters

TABLE 10

PROTOCOLS OF 3 FATAL CASES

	KUM 7	KUM 29	Kum 23
AGE	17	28	35
SEX	Female	Male	Male
Distance from center, meters	500	1000	1500
Type of building	Factory	Factory	Wooden Hse
Other Injuries	None	None	Burns
Epilation	Yes	Yes	Yes
Purpura	Yes	No	No
Oropharyngeal Lesions	Yes	No	Yes
Blood Exam.(see figure 3)	-	-	-
Marrow Examination. Total Nucleated cell count-	800	2950	5150
'Blasts	0.4	0.3	2.0
Promyelocytes	0.2	0.9	7.2
N.Myelocyte	-	1.1	1.6
N.Metamyelocyte	0.2	1.6	10.8
N. Stab Form	0.4	10.8	15.6
N. Poly	2.8	26.5	3.2
Eosinophil (all)	2.6	11.7	2.8
Lymphocyte	64.0	41.5	28.4
Monocyte	-	-	-
Histiocyte	1.8	0.5	3.6
Plasma Cell	22.4	0.9	13.2
Erythroblast	1.4	0.4	0.2
Normoblast	3.8	3.8	10.6
Myeloid:Erythroid Ratio	1.3:1	12.6:1	4.0:1

24 (7)

and 1000 meters, respectively. The other was in a wooden building at 1500 meters. The relevant clinical data and the results of examination of the blood and the bone marrow are presented in Table 10 and summarized in Figure 3. These three cases are particularly interesting because on the same date - 26 days after exposure to the gamma rays, each had a quite different and quite distinctive type of marrow. In the other case records that follow, examples will be shown of patients who survived and who had some one of these same types of reaction in the marrow in the early stage of the disease. This point is worthy of emphasis if only to hinder the formation of fixed ideas of the relative seriousness of one or another type of marrow reaction.

(1) Case KUM 87. Male, 33, 1200 meters (Nagasaki)

Patient was in a wooden house which collapsed, trapping him under it. He sustained only minor lacerations of the arms. Epilation of the scalp commenced 15 August. This was followed by pharyngitis, gigivitis, and purpura. He was treated at a hospital with frequent transfusions from 11 September to 20 September. He was discharged from the hospital in good condition on 19 October.

EXAMINATION OF THE BLOOD	Hb.	RBC	WBC	Platelets
9 September	-	-	1900	-
11 September	44%	2.25	1170	29,000
17 September	39%	1.75	2600	-
24 September	50%	2.96	4450	1,115,000
1 October	59%	2.90	6780	
10 October	69%	3.28	13100	

Differential Counts.

	Stabs	Polys	Lymph.	Mono.	Eosin.	Plasma
9 September	3	6	74	5	7	3
11 September	3	5	85	4	3	-
*17 September	20	6	62	8	2	2
24 September	12	25	48	6	7	2
1 October	10	25	40	13	12	-
10 October	8	9	39	3	41	-

*A few metamyelocytes were seen.

Additional Laboratory Data. Reticulocytes varied from virtually none on 11 September to 7.7% on 24 September. The longest bleeding time was recorded as 16 minutes on 9 September; and the longest clotting time was 14 minutes 30 seconds on the same day.

Examination of bone marrow.

The results of the three biopsies of sternal marrow are presented in Table 11 and are summarized in Figure 4. (See also figure 18).

(2) Case KIU-48 Female, 19, 1200 meters (Nagasaki).

Patient was standing in a wooden, earth-covered shelter which collapsed. She sustained mild unspecified injuries. During September she had an ulcerative gingivitis. There was no epilation. She was treated in the hospital with liver extracts and iron and was discharged as cured 19 October 1945.

Laboratory Data.

Date	HB	RBC	WBC	
8 September	63%	2.66	1200	
10 September	32%	2.32	1000	
18 September	42%	2.50	2400	
21 September	60%	1.47	2400	
24 September	65%	2.96	5600	No other data are avail-
27 September	63%	3.10	4600	able on this patient.

TABLE 11

KUM 87

DIFFERENTIAL COUNT OF STERNAL MARROW

	11 September	14 September	19 September
'Blasts	1.4	4.2	8.0
Promyelocyte	8.2	15.5	13.4
N. Myelocyte	1.0	1.7	5.7
N. Metamyelocyte	2.8	6.0	12.5
N. Stab Form	2.6	3.9	20.0
N. Poly	0.6	0.5	6.0
Eosinophil (all)	2.4	2.6	16.0
Lymphocyte	48.0	23.2	2.9
Monocyte	-	0.3	-
Histiocyte	8.0	6.3	0.3
Plasma Cell	14.2	8.7	0.4
Erythroblast	2.0	3.2	0.8
Normoblast	8.2	21.8	11.0
Myeloid:Erythroid Ratio	1.9:1	1.4:1	8.2:1
Total Nucleated Cell Count	17,300	17,800	68,000

Laboratory Data-continued

Date	Hb	RBC	WBC
30 September	60%	2.25	6300
3 October	65%	2.22	3800
7 October	65%	2.25	5800
10 October	65%	2.50	7000
19 October	74%	4.50	7000

Examination of bone marrow.

The results of two biopsies of sternal marrow are presented in Table 11A and are shown in Figure 5.

(3) Case H-6030-U, Male 24 1000 meters (Hiroshima)

Patient was inside a wooden building. He sustained no injury except by radiation. Epilation occurred 15 August and he entered hospital 26 August. Purpura was observed on 27 August, and ulcerative oropharyngeal lesions developed early in September. He was discharged as cured 2 October 1945.

Laboratory Data.

Date	Hb.	RBC	WBC
7 September	90%	3.36	700
10 "	-	-	1500
1 "	-	-	2400

The differential count on 7 September was:

Metamyelocytes	4%
Polys	40%
Lymphs	52%
Monocytes	4%

Examination of bone marrow.

The results of three biopsies of sternal marrow are shown in Table 11B and are summarized in Figure 6.

(4) Case H-6010-U: Male, 28, Less than 1000 meters. (Hiroshima)

Patient was indoors in a Japanese building which collapsed on his head, rendering him unconscious for an unspecified length of time. Epilation commenced 17 August. He entered the hospital 28 August. Petechiae appeared

TABLES 11A and 11B

DIFFERENTIAL COUNTS OF STERNAL MARROW

	Table 11A-KIU-48		Table 11B--H-6030-U		
	11 Sept.	5 Oct.	7 Sept.*	26 Sept.	16 Nov.
Blast	1.2	0.4	-	1.3	2.4
Promyelocyte	1.2	0.4	-	1.3	3.7
N. Myelocyte	15.1	4.6	-	1.3	5.7
N. Metamyelocyte	17.5	17.0	6.3	6.5	16.2
N. Stab Form	10.5	42.0	6.3	17.7	18.0
N. Poly	2.9	2.7	6.3	28.1	20.1
Eosinophil Cell	0.8	2.7	-	-	8.1
Lymphocyte	18.8	5.0	75	12.4	6.9
Monocyte	2.4	1.4	5	1.3	1.6
Histiocyte	2.4	-	-	0.7	1.2
Plasma Cell	14.8	0.4	-	2.0	0.4
Erythroblast	2.1	3.0	-	3.2	2.8
Normoblast	9.6	21.0	-	23.5	13.4
Myeloid:Erythroid Ratio	4.2:1	2.9:1	-	2.1:1	4.5:1
Total Nucleated Cell Count	33,000	211,000	3,800	-	-

*This was a poor preparation-only 19 recognizable cells could be found.

1 September, and pharyngitis and gingivitis developed about 5 September. He recovered, but the date of discharge from hospital is not known.

Laboratory Date.

Date	Hb	RBC	WBC	Platelets
3 September	90%	4.15	1200	-
8 "	-	-	2200	-
13 "	-	-	2200	-
19 "	56%	3.29	1000	70,000
24 "	56%	3.45	4100	-
17 November	98%	5.23	8600	73,000

Differential Counts.

19 September: Stabs-14; Polys- 35.5; Lymphs. 34.5; Mon. 13.5; Eos. 2.5

17 November: Stabs-10; Polys- 40; Lymphs-39; Mono.-1; Eos.-9; Baso.-1.

Examination of bone marrow.

The results of three biopsies of sternal marrow are presented in Table 12A and are summarized in Figure 7.

(5) Case H-6016-U Male, Age unknown Less tha 1200 meters (Hiroshima)

Patient was indoors in a Japanese building. He received no injuries except by gamma radiation. Epilation and purpura commenced 20 August; and gingivitis and pharyngitis developed early in September. Ultimately, he recovered.

Laboratory Data.

Date	Hb	RBC	WBC
5 September	70%	3.66	1800
8 September	-	-	6400
14 September	-	-	5500

TABLES 12A and 12B

DIFFERENTIAL COUNTS OF STERNAL MARROW

	Table 12A--H-6010-U 4 Sept.	24 Sept.	17 Nov.	Table 12B--H-6016-U 6 Sept.	22 Nov.
'Blast	-	0.6	0.8	4.1	3.0
Promyelocyte	-	0.6	0.4	6.1	0.5
N. Myelocyte	-	1.2	0.4	6.1	2.0
N. Metamyelocyte	0.6	15.0	0.8	13.0	13.5
N. Stab Form	2.4	32.2	6.2	39.5	24.0
N. Poly	15.8	6.0	14.7	8.5	8.5
Eosinophil (all)	4.8	4.8	8.3	-	4.5
Lymphocyte	45.1	11.3	40.4	2.0	5.0
Monocyte	2.4	1.8	4.0	15.8	4.5
Histiocyte	-	-	-	0.6	0.5
Plasma Cells	-	1.2	-	2.6	1.5
Erythroblast	-	4.2	1.2	-	1.5
Normoblast	28.9	21.1	22.8	1.3	25.00
Myeloid:Erythroid Ratio	0.8:1	2.7:1	1.3:1	-	1.8:1
Total Nuclear Cell Count	2,000	-	73,000	3,800	-

The Differential Counts on 5 and 8 September were:

	5 September	8 September
Myelocyte	6	3
Metamyelocyte	14	9
Stab Form	14	18
Poly	52	48
Lymphocyte	14	22

Examination of bone marrow.

The results of two biopsies of sternal marrow are presented in Table 12B and are summarized in Figure 8.

(6) Case KIU-49 Male, 35 1000 meters (Nagasaki)

Patient was standing in a brick factory building but sustained neither burn nor mechanical injury. From 7 to 21 September he had a pharyngitis. There was no epilation nor any purpura. Recovery was satisfactory.

Laboratory Data.

Date	Hb	RBC	WBC	
13 September	45%	2.70	2100	
17 September	42%	2.42	3000	
20 September	62%	3.53	1600	
23 September	54%	2.64	1800	No other laboratory data were available.
26 September	65%	2.80	2600	
29 September	64%	2.25	2400	
4 October	62%	2.35	3300	

Examination of bone marrow.

The results of four biopsies of sternal marrow are presented in Table 13 and are summarized in Figure 9.

TABLE 13

DIFFERENTIAL COUNT OF STERNAL MARROW

CASE KIU - 49

	12 Sept.	14 Sept.	21 Sept.	5 Oct.
'Blast	0.9	-	-	-
Promyelocyte	0.9	-	1.0	1.0
N. Myelocyte	10.0	13.0	2.0	10.00
N. Metamyelocyte	15.0	25.0	10.0	22.0
N. Stab Form	9.0	22.0	25.0	27.0
N. Poly	3.5	4.0	7.0	5.0
Eosinophile (All)	8.5	2.0	-	2.0
Lymphocyte	29.1	20.0	40.0	5.0
Monocyte	2.2	2.0	1.0	-
Histiocyte	-	-	1.0	-
Plasma Cell	7.8	4.0	8.0	4.0
Erythroblast	0.4	1.0	1.0	2.5
Myeloid:Erythroid Ratio				
Total Nucleated Cell Count	5,000	8,400	34,200	202,000

(7) Case H-6025-U Male 24 1000 meters (Hiroshima)

Patient, an army surgeon, was inside a frame hospital building. He was knocked down by the blast but sustained no injury. Epilation of the scalp commenced 21 August. He was hospitalized 25 August. Gingivitis appeared 23 August and by 6 September he had an ulceration of the hard palate. Petechiae were noted first on 27 August. On 3 October he was sufficiently recovered to leave the hospital.

Laboratory Data.

Date	Hb	RBC	WBC	Platelets
6 September	45%	2.01	1300	-
11 September	-	-	3800	-
16 September	-	-	4800	-
21 September	67%	3.18	4000	110,000
27 September	57%	3.10	6500	130,000
15 November	70%	3.00	-	102,000

Differential Counts. Differential counts on several occasions were as follows:

	21 Sept.	27 Sept.	15 Nov.
Stab form	17.0	11.5	4.0
Poly	49.5	63.0	37.0
Lymphocyte	20.5	15.5	44.0
Monocyte	9.5	6.0	12.0
Eosinophil	3.5	3.0	3.0

Examination of bone marrow.

The results of three sternal marrow biopsies are presented in Table 14 and are summarized in Figure 10.

TABLE 14

DIFFERENTIAL COUNT OF STERNAL MARROW

Case H - 6025 - U

	6 September	27 September	12 November
Blast	2.5	1.5	2.0
Promyelocyte	1.7	1.5	3.0
N. Myelocyte	8.7	3.1	5.0
N. Metamyelocyte	10.6	10.5	10.4
N. Stab Form	25.0	16.8	27.0
N. Poly	15.6	16.8	7.0
Eosinophil (all)	-	3.6	1.6
Lymphocyte	3.4	11.0	9.0
Monocyte	6.2	1.5	2.5
Histiocyte	0.8	-	-
Plasma Cell	1.7	-	0.4
Erythroblast	6.2	3.6	3.5
Myeloid-Erythroid Ratio			
Total Nucleated Cell Count	4,500	-	174,000

CYTOLOGY OF BONE MARROW

General.

In this section, an attempt will be made to describe comprehensively the reaction of bone marrow to large doses of gamma radiation. A detailed cytological analysis of every case, and of all the variations to be found, would be desirable but would result in a study too large for the scope of this Report. It will be imperative to confine the discussion to a simple presentation of general principles deduced from a study of representative cases. Necessarily, because the smears made from material obtained by biopsy fail to show the relationship of cells, reference will be made to the histologic material. In general, the discussion will be confined to cases where there is reason to believe that the gamma radiation destroyed practically all the definitive elements of the bone marrow. This qualification is desirable if the intimate details of regeneration are to be studied, for in less severely radiated patients the process of recovery may be rendered very complex by the presence of cells that presumably survived injury in association with newly formed elements. It would have been most desirable to base the presentation entirely on material from patients whose only injury was by gamma rays. Similarly, the study would have been more valid scientifically if the patients had not been subject to severe and often overwhelming infections. Since these conditions were obviously impossible of realization, and since it was indicated in Table 7, page 17, that the complications had little apparent influence on the reaction of the marrow, the cases have been selected for discussion solely because there was good evidence of severe injury. Nevertheless it must be appreciated that infection, blood loss and nutritional deficiencies may have affected to a considerable degree the processes to be described. An understanding of the regenerative process in the marrow is simplified if the question of the dosage of gamma radiation i.e., the location of the victim with respect to the center of the explosion, and with regard to possible shielding factors is disregarded. It should suffice to say that all the patients under discussion probably received sufficient radiation to destroy "almost all" the definitive elements of the bone marrow, in fact, this assumption has been the basis of the selection of illustrative cases in this section.

The effect of gamma rays on bone marrow.

It is known from experiments with animals, and from studies of human beings accidentally or therapeutically exposed, that the bone marrow is one of the most radio-sensitive tissues of the body. It is also known that the myelopoietic, the erythropoietic and the thrombopoietic systems (the definative elements) are more susceptible to ionizing radiation than are the other structures of the marrow. These less sensitive portions include the fibrous tissues, the vascular tissues, the fat, and the reticulo-endothelial system. On the basis of the foregoing it is possible to postulate three degrees of response to varying intensities of radiation, as follows:

1. Complete destruction of the definitive elements and the reticulo-endothelial system.

2. Complete destruction of the definitive elements, with partial or complete sparing of the reticulo-endothelial system. After such a dose of ionizing radiation, the subject should have the capability of recovering.

3. Partial destruction, or damage, to the definitive elements of the marrow.

After injury to the bone marrow by radiation the granulocytes and the platelets in the blood are found to be decreased in number. It is reasonable to conclude that the severity of the leukopenia and the thrombopenia should parallel the severity of the damage. These changes develop quite frequently, as has been shown in Section 6. The effect of the radiation on the erythrocyte count is manifested more slowly because of the longer life span of the individual cell. By the same sort of reasoning it is logical to conclude that increasing numbers of granulocytes and platelets in the blood are indicative of recovery of the bone marrow. Unfortunately, the laboratory studies have not been very complete in all the cases, but it is possible to piece together a general interpretation from the details that are available.

On page 2 where the objectives of the study of the marrow were stated, the third item was the determination of the rate of disappearance of definitive cells from the marrow. The two earliest sternal biopsy specimens were obtained from Hiroshima. Both patients had been in the Banker's Club, a reinforced concrete building, located approximately 200 meters from the center (See Section 11H). The details were as follows:

(8) Case H-10615-I Male 30. Sternal biopsy was performed 11 August. The white cell count on that day was 400 per cubic millimeter; and on 14 August, the day of death, it was 100. On the entire blood film made 11 August, only 8 leukocytes were seen; 6 polys with abnormal appearing granules; and 2 small lymphocytes. There were no blood platelets. The differential count of all cells seen in the marrow smear was:

Polys	3
Small lymphocytes	5
Histiocytes	29
Plasma Cells	19
Unidentifiable cells	44
Total	96

(9) Case H-10645-I Male 31. Sternal biopsy was performed between 12-15 August. There were too few cells to count. The forms seen included a few plasma cells, a few degenerating metamyelocytes and a few small lymphocytes. A blood film made at about the same time was available for examination. Three cells were found: 2 polys and 1 small lymphocyte. There were no platelets.

The specimens of bone marrow from the earliest autopsies are discussed in detail in the section on Pathology. Suitable material from a patient who died on the 6th day after the bombing shows complete absence of all granulocytic cells except for a few eosinophils. There were no megakaryocytes; and only small groups of nucleated red cells were present. It would be impossible to say whether or not the eosinophil and normoblasts were survivors, but this seems probable. The significant feature of this early marrow is the finding of proliferating reticulum, as well as small numbers of lymphocytes, plasma cells and histiocytes.

THE PATTERN OF REGENERATION

The knowledge that the normal blood cells disappeared quickly and practically completely from the marrow of patients exposed to the intensities of gamma radiation emitted by atomic bombs simplifies the study considerably. No significant error should result from the assumption that at some period of time, of the order of one to two weeks, practically all the normal definitive marrow elements will have disappeared from the tissues of patients with the characteristic symptomatology of severe radiation sickness. Even more useful is the evidence for the correctness of assuming that within the same period of time the reticulo-endothelial elements of the marrow will have started to multiply, and to produce certain types of cells. With this background it is possible to proceed with a description of the types of cells which were found in the marrow of patients with symptoms of severe radiation injury with considerable certainty that the phenomena observed are in fact regenerative. The term "regenerative" is used here in the sense that the phenomena to which it is applied represent the formation of definitive marrow cells by some other process than by a multiplication of surviving members of the definitive families. This is an important distinction to make if the findings in marrow of irradiation subjects is to be interpreted correctly. It is perfectly proper to recognize that both processes: regeneration and multiplication of surviving definitive cells, may coexist in a given case.

There is nothing particularly novel on the one hand, in the hyperplasia of normal marrow cells in response to any stimulus. On the other hand, the opportunity to observe, in many similar cases, the regeneration of marrow which has lost all or nearly all the ordinary definitive elements due to a single instantaneous insult, is distinctly unique. Accordingly, the emphasis throughout the description that follows will be placed on the pattern of the regeneration insofar as it can be determined from a study of histological preparations and smears.

The types of reaction which have been observed can be classified into several groups (See table 15) which will be considered separately:

TABLE 15

Group 1. Proliferation of reticulo-endothelium.

Group 2. Proliferation of reticulo-endothelium plus proliferation of certain mononuclear cells:

a) Macrophages
b) Plasma cells
c) Lymphocytes

Group 3. Metamorphosis of "reticular marrow" into definitive marrow.

Table 15-continued.

Group 4. Evolution of the newly formed definitive marrow:

A. The myeloid elements.

a) "Myelocytic marrow"
b) "Metamyelocytic marrow"
c) "Shift to the left"
d) "Regular or normal appearing marrow"
e) "Eosinophilic marrow"

B. The erythroid elements

C. The Megakaryocytes

Group 5. Unsatisfactory evolution of the "reticular marrow."

a) Inadequate numbers of cells
b) Abnormal types of cells

Group 1. Proliferation of reticulo-endothelial system: This type of activity has been seen regularly in every marrow specimen obtained during the first 3-6 weeks after severe injury by ionizing radiation. There is no example where it is the sole process to be seen in the tissues. In every case which has been examined there have been some areas in the tissue where the mononuclear cells (see below Group 2) are found in association with the proliferating reticulum. Regardless of this fact, it is possible to describe and illustrate the characteristics of the process. In smears of sternal marrow the cells which are designated as reticulum are large with abundant cytoplasm (See figures 11 and 12). The cytoplasm is non-granular, and is palely basophilic with a ground-glass texture, or a flocculent appearance. The nucleus is variable in shape. In the earliest stages it is oval and may be slightly indented, later (i.e., more mature forms) have round nucleus. The size is also variable, from quite small (approximately the size of the examples shown in Figure 11) to 2 or 3 times as large. The structure of the nucleus is characteristic: The nuclear membrane is indistinct. The chromation occurs in fine threads, loosely arranged into a delicate network, with a few small and comparatively inconspicuous nucleoli. In fixed tissues the reticulum is first recognizable as "swollen" elements in the walls of the sinusoids, or branching or "budding" off from the walls either into the spaces between them and the fat cells, or into the lumen of the sinusoids. Early, the cells have a stellate configuration (See figures 13 and 14) (Key 39*). Later, one gets the impression that these cells "round up" and form into "free" cells in the tissue spaces. In tissues, the vesicular quality of the nucleus is conspicuous, with one or several small nucleoli and a fine nuclear membrane. Throughout all the tissues of this period small numbers of multinuclear reticulum cells can be found. In some cases the several nuclei are normal in appearance. In others they are unequal, or abnormally large, or otherwise unusual. In general, this type of cell has distinct, condensed cytoplasm, and has the appearance of a free cell, rather than that of a component of the reticulum network. The resemblance of these forms to the so-called Reed-Sternberg cell is often striking. In other cases they resemble "young" megakaryocytes.

With special stains, the abundant cytoplasm contains no granules, and is lightly basophilic. In the majority of the cases autopsied or biopsied between 12 August and, say 15 September, in either city, there is some evidence of proliferation of the reticulum. It is to be seen occurring typically, in the "islands" between the fat cells and the sinusoids, and in close

*Key number refers to autopsy protocol. (See Section on Pathology for details.)

proximity to small blood vessels. As was mentioned above, the usual situation was the occurrence in any given case not only of regions of proliferating reticulum, but also regions where mononuclear cells are associated with it.

Group 2. Proliferation of reticulo-endothelium plus the proliferation of certain mononuclear cells.

This type of reaction in the bone marrow was the most typical finding in specimens obtained from patients with the syndrome of severe radiation injury in the period, 26 August to 11 September, or approximately during the 4th and 5th week after exposure to the gamma rays. Fortunately, it was also during this same period that Japanese physicians were studying the patients most intensively, so that many biopsy and autopsy preparations are available for examination. The time interval is not only the same one in which the most striking clinical symptoms occurred (See Section 5), but also the one in which the mortality rate due to radiation injury, primarily, was the highest. The frequency of this type of reaction in the biopsies performed at this period, and obtained by the Joint Commission was: for Hiroshima, 8 of 35; and for Nagasaki, 17 of 42 cases.* Total counts of nucleated cells in all the marrow punctates were low (see table 5, page 13), and in cases where this pattern was found, the average value was less than 10,000 cells per cubic millimeter.

*The numbers of these cases are: H-6001-U; H-6003-U; H-6007-U; H-6008-U; H-6012-U; H-6014-U; H-6030-U (See also Section 4.7, third case record); and H-12096-OSK (Hiroshima cases). KUM 4,5,7,8,10,16,17,43; KIU-2,4,41, 42, 43, 44, 45, 46, 47 (Nagasaki cases).

The combination of proliferation of the reticulo-endothelium and a variety of mononuclear cells: Macrophages, plasma cells and lymphocytes, has been described by Rohr, (loc. cit.) in cases of agranulocytosis and aplastic anemia, and has been designated by him a "reticular marrow". This situation as it was encountered in the study of the Japanese material differed in only one respect from the conventional descriptions, namely small foci of erythropoiesis were found in many cases; and these were frequently the only type of definitive cell to be seen in significant numbers. Although in any one case it was usual to observe varying numbers of each of the four types of mononuclear cell, it is convenient to describe examples where one variety or another predominated. Such a practice will also permit the presentation of illustrations showing the genesis of the several forms.

A. Macrophages: Typical macrophages were a conspicuous feature of all the "reticular marrows". In some smears from biopsy material as many as 51% of the nucleated cells are macrophages (or histiocytes), a varying number of which contained pigment. The presence of these phagocytic cells was especially striking in the autopsy material, and a description of representative tissues will be found in the section on Pathology. In the tissues the macrophages frequently were seen to contain erythrocytes; but this was an unusual finding in the smears of aspirated marrow. The typical appearance of these pigment-containing cells in smear preparations is seen in Figure 15. The relationship between the macrophages and the proliferating reticulum is well illustrated in Figure 16 (tissue from Key #34) where there is little apparent difference between the nuclei of the reticulo-endothelial cells and of the erythrocyte-containing macrophages.

B. Plasma Cells: All stages and shapes of plasma cells were a constant finding in the marrows obtained at any time. The largest numbers were observed in the 4th to 5th week after irradiation, and in differential counts of sternal marrow percentages in excess of 20% were not uncommon (See Case KUM 7, table 10, page 24). The average percentage of plasma cells in the differential counts for the period 1-14 September was 2.7% in the Hiroshima and 11.0% in the Nagaskai material, respectively. In stained films of marrow the plasma cells were quite conspicuous and were very typical in appearance (figures 17 and 18). In the histological preparations they were seen quite generally, and appeared to occur in two situations with about equal frequency when appropriate material was examined. One situation is illustrated in Figure 19 where the plasma cells can be seen in an "island" of proliferating reticulum, in association with that type of cell, and with lymphocytes. Here it would be difficult to judge whether the plasma cells were formed there, or were carried there by the circulation. The other situation is shown in Figures 20 and 21, (Key # 21, died 30 August 1945). In these sections the plasma cells can be seen arranged in a row or a string and apparently attached to, if not derived from, a band of endothelium which forms quite definitely the wall of a sinusoid. (See figure 20.) In Figure 21, there appears to be a bifurcation of the endothelium, with the formation on a small island, and all the cells associated therewith are plasma cells of various stages. This latter situation was commonly observed in many of the tissue sections, and seems to offer good evidence for the autochthonous origin of plasma cells from reticulum in the marrow. This observation is not intended to convey the impression that marrow reticulum is the only source of plasma cells, or even the only source in patients injured by gamma radiation. The same type of development of plasma cells, in "strings" associated with reticulo-endothelium may be seen in the spleen and lymph nodes of these patients.

C. Lymphocytes: Almost all the samples of "reticular marrow" obtained in the critical period when the symptoms of radiation sickness were most pronounced contain large numbers of lymphocytes. An examination of the average differential counts for the period 1-14 September reveals that this was the most numerous single type of cell. (See table 9, page 20). The average percentage of lymphocytes at that time was 28.6% for Hiroshima, and 40.2% for Nagasaki cases, respectively. In individual patients, values as high as 80% were observed. The majority of lymphocytes seen in marrow obtained by puncture were quite ordinary appearing small lymphocytes. However, in many of the cases a variable number of large abnormal lymphocytes were seen. The number of marrow specimens which were found to have significant numbers (i.e. more than 1%) of the abnormal lymphocytes and the time-periods when they were found is shown in Table 16. In summary, the incidence of this finding was 56% for Hiroshima, and 31% for Nagasaki cases, respectively. In general, these were very large cells (See figures 22,23,24) with certain common characteristics. The cytoplasm was abundant, usually flocculent, and basophilic. With the Romanowsky type of stain, it was a grey-lavender in color, and typically it contained no granules. This last statement requires a qualification: This abnormal lymphocyte did not have cytoplasmic granules in forms presumed to be "young". In "older" cells, as judged by the nuclear structure, two changes were apparent. The cytoplasm became darker in color, and azurophile granules appeared in it. (See figures 25, 26, 27.) The result, depending on the intensity of each process, was a cell which resembled in some cases the monocytes of the blood; and in other cases neutrophilic myelocytes. In some preparations the differentiation of such mononuclears was exceedingly difficult and often quite impossible. The structure of the nucleus was generally quite specific and permitted recognition of the cell as a lymphocyte. In the youngest types the chromatin was fine, often almost reticular in quality (See figure 23). In other stages the chromatin formed rather broad clumps (See figures 22,24,28) and in the later stages it was even coarser in quality, although the contrast with parachromatin tended to decrease. (See figures 25, 26, 27). In the tissues obtained at autopsy, lymphocytes were likewise conspicuous. In the less advanced stages of regeneration lymphocytes were regularly seen in close association with the proliferating reticulum and the developing plasma cells, as for example in Figures 19 and 29. (Key # 23, died 31 August 1945.) Another example of this association which suggests the local genesis of the larger lymphocytes is discussed in Section 8 (Key # 29, died 1 September 1945). In both these cases, large lymphocytes with reticular-type nuclei can be seen in the "islands" where the regenerative activity is concentrated. The appearance of lymphocytes in association with larger groups of reticulum and plasma cells is seen in the autopsy case, (See Section 8, Key # 28, died 1 September 1945.) The identification of the large mononuclears as abnormal lymphocytes in this case is supported by the Giemsa-stained smear (see figure 28.). A few examples of the apparent development of "strings" of lymphocytes from bands of endothelium, or by the rounding up of the cells in the walls of sinusoids were observed. This phenomenon was seen sufficiently frequently to add support to the impression gained from other findings as to the autochthonous origin from the reticulo-endothelium of some of the lymphocytes found in the marrow of irradiated patients. Just as in the case of the plasma cells this is not to say that the marrow is the sole source of these lymphocytes; but the evidence is quite strong that the large abnormal lymphocytes may devlop there directly from reticulum. In none of the tissues at this stage was there observed any indication of the transformation of lymphocytes into plasma cells, or vice versa.

TABLE 16

ABNORMAL LYMPHOCYTES IN BONE MARROW BIOPSY SMEARS

HIROSHIMA			NAGASAKI	
TOTAL CASES	ABNORMAL LYMPHOCYTES PRESENT	TIME	TOTAL CASES	ABNORMAL LYMPHOCYTES PRESENT
22	18	1-14 Sept.	23	16
6	1	15-30 Sept.	3	1
9	3	1-15 Oct.	19	3
10	5	16-31 Oct.	59	5
12	6	November	22	12
-	-	December	12	6
33	59	Totals	138	43

D. Nucleated Red Cells: Many of the histological specimens of marrow obtained in this early stage contain small groups of what appear to be nucleated red cells. In the stained films of marrow from biopsy, the identification of these cells is verified. The average value for nucleated red cells in biopsies performed during the first 2 weeks of September (the 4th & 5th week after the bombing) was found to be 13.4% for Hiroshima, and 9.9% for Nagasaki cases, respectively (See table 9, page 20). The significance of these erythropoietic foci is difficult to determine. Their appearance is clearly shown in Figures 30 and 31, (Key # 32, died 2 September) and in a number of examples in the Pathology section: (Key # 29 and # 24, etc.)

In all these specimens the nucleated red cells are seen to occur in small groups generally in close association with the proliferating reticulum; and in many instances they appear to be located in the meshwork formed by these cells. There does not appear to be any consistent pattern with respect to the location of these younger cells in relation to the sinusoids. The nuclei were generally pyknotic, and were often formed into abnormal karyorrhectic figures. So far as can be seen in the histologic preparations the cytoplasm appears to contain hemoglobin. This impression is supported by examination of the smear preparations, in which the majority of the nucleated red cells may be classified as polychrome and orthochrome normoblasts. Immature basophilic erythroblasts are seen infrequently at this stage. Numerical evidence for this observation is found in the differential counts of sternal marrow for the period 1-14 September, where the ratio of erythroblasts: normoblasts is as low as 1:8. (Normal values range from 1:6 to 1:4), in the Nagasaki series. The problem that is presented by the findings of these cells is simply whether they are: a) normoblasts which have survived the gamma radiation; or b) cells newly formed during the process of recovery. The point is principally academic, but is of interest, for the nucleated red cells are not an uncommon finding at a stage of recovery before the reappearance of myelopoiesis. It seems most probable, however, that they should properly be considered as survivors.

E. Miscellaneous: Megalokaryocytes were quite scarce in the so-called reticular marrows. The multinucleated reticulum cells referred to above often resembled them to a marked degree; and it may be that many of these types were in fact young forms. It is a safe generalization, however, that megalokaryocytes of the ordinary adult type were very rare.

Group 3. Metamorphosis of "reticular marrow" into "definitive marrow".

It has been shown that in the marrows depleted by gamma rays there was an early and comparatively abundant proliferation of the reticulo-endothelium. The process commenced within 7-14 days after irradiation and resulted in the formation of what has been described as a "reticular marrow". This pattern prevailed for a period of 2 to 3 weeks, and during this time profound leukopenia was regularly observed when the blood was examined. In patients who survived, the blood count was found to increase, and the time at which the increase began was quite variable. (See Section 6), but generally commenced about 3-4 weeks after the bombing. The changes which occurred in the bone marrow just prior to and concurrent with the reappearance of granulocytic cells were very interesting. In specimens obtained at appropriate times it was possible to observe a phenomenon which may be described as the metamorphosis of "reticular marrow" into definitive marrow. In the biopsy material available for study, which was obtained in the period 1-14 September, this transformation was observed in 10 of 35 cases from Hiroshima and in 15 of 42 cases from Nagasaki.* The reaction was seen in cases with scanty proliferation of the reticulum as well as in those with a profuse reaction. Two distinct patterns were observed, although in given cases, it was usual to observe both occurring simultaneously. It is convenient, however, to describe the processes separately.

*The numbers of these cases are: H-6010-U; H-6011-U; H-6026-U; H-6028-U; H-6029-U; H-6030-U; H-6031-U; H-6032-U; H-6038-U; H-11879-KPS
See also: H-6024-U; H-6043-U; H-6063-U; and H-6311-P, where the process was observed at a later time.
See also: AMM 158930-86 and 107 for autopsy specimens (Hiroshima cases). KUM 18 23, 39, 42; KIU-1, 3, 5, 6, 7, 8, 19, 21, 45, 46, 47 (Nagasaki Cases).

a) The commonest pattern was the metamorphosis of reticulum cells into granulocytes. The reticulum cell which underwent this development was usually quite large with abundant, nongranular, deeply basophilic cytoplasm, which characteristically was paler in the region adjacent to the nucleus. The nucleus was often excentric and was usually round, or somewhat indented. The chromatin threads were moderately fine (but less so than in the conventional 'blast), and were arranged in a distinctly reticular, or net-like manner. The nucleoli were small, prominent, and often encircled by a conspicuous ring of chromatin. A very characteristic example of such a cell is shown in Figure 12. Other examples will be discussed presently. In histological preparations, the cell was obviously a free cell, distinctly rounded, and the nuclear structure was definitely intermediate in quality between that of the reticulum cell, and that of the myelocyte. The process of transformation was recognized by the appearance in these rounded-up free reticulum cells of azurophile granules. This was followed by the appearance of neutrophilic or eosinophilic specific granules. It was not until the cell had acquired a considerable amount of granulation that the nucleus lost its reticular quality. The chromatin ultimately became coarse and condensed, and then resembled closely that of the conventional metamyelocyte. The series of changes, and the appearance of the cell-types is shown in the series of photomicrographs: (See figure 12 for the typical reticulum cell.) In figures 32 and 33,)Key #43, died 7 September, 1945) is shown this same type of cellular change in two groups of cells stained with Wright-Giemsa from imprint preparations. Here in groups of very similar appearing cells, can be seen several degrees of azurophil granulation of the cytoplasm. In figure 34,(Key #22, died 31 August 1945,) the same type of differentiating reticulum cell is shown in tissues stained with Giemsa. Imprint preparations of this marrow, Figures

35, 36, 37 show groups of large, free reticulum cells, some of which contain a few fine azurophile granules. These figures show clearly the contrast between the ordinary reticulum cell and the rounded, free type which appears to participate in the metamorphosis. Figure 38 shows another group of cells with many gradations from no granules to the presence of both azurophilic and neutrophilic ones. The progressive maturation of the nuclear structure is well illustrated in this series.

b). The other pattern which was observed was the same process of progressive development of granulation, but in this case the cell which underwent metamorphosis was an abnormal lymphocyte of the type described and pictured in a preceding section. The metamorphosis of this large abnormal lymphocyte was never seen to be the principal process occurring in any case. However, it was a frequent finding, and the identification of the cells in the early stages of transformation was difficult. The principal differences between the two series were as follows: In the case of the abnormal lymphocytes, the azurophile granules were fewer and smaller, and the cells in which they appeared seemed to develop a sparse type of neutrophil granulation so that their appearance was never quite typical of a granulocyte. The nuclear structure became coarse even when the granulation was scanty; and "stab-like" forms were seen in which the cytoplasm retained the lavender qualities of the abnormal lymphocyte. A number of examples of this variety of metamorphosis are offered, beginning with a very early example, (See figure 25) where the first faint, small azurophile granule can be seen in a large abnormal lymphocyte. The difference between the nuclear structure of this cell, and that of the cells in Figure 38 or Figure 36 is quite apparent. In Figures 27 and 26, the denser quality of the nucleus and the failure of development of characteristic neutrophilia is evident. The granule-containing cells in Figure 39 show again the persistence of the typical cytoplasm of the abnormal lymphocyte. These cells have more azurophile granules than usual, but it will be seen that they tend to collect at the periphery of the cell. Figure 40 is another comparable example, and is of interest because this specimen was obtained much later in October, 10 weeks after the bombing. The same is true of the specimen in Figure 41 which was collected in December, showing the persistence of the abnormal lymphocytes in the marrow, with good evidence that some of the granulocytopoiesis is occurring in this manner.

As a contrast to these types of metamorphosis of the "reticular marrow", it will be helpful to present two illustrations of marrow in which the majority of myelopoiesis is occurring in the conventional manner with 'blasts as the youngest member of the series to be recognized. Figure 42 is from patient KIU-49 (See (6) Case, page 32) **and** was known to have had a "reticular marrow" several weeks earlier. Figure 43 is a photomicrograph of a biopsy obtained early in October (Case 278, Nagasaki) which was conspicuous for the large number of 'blasts that were seen.

It would be difficult to state with any degree of certainty how frequently one or the other of these patterns of metamorphosis occurred. There is no reason at all, of course, to doubt that in many instances the reticulum cell may have differentiated into 'blasts, which in their turn produced a definitive marrow. The random manner in which biopsies were made has left many gaps in the material available for study. In spite of such drawbacks, it seems quite certain that there are at least three ways in which the marrow may recover from the sort of injury that was caused by the gamma radiation of the atomic bomb:

a) Metamorphosis of reticulum into myelocytes.

b) Metamorphosis of abnormal lymphocytes, (which were themselves derived from reticulum) into myelocytes.

c) Metamorphosis of reticulum into 'blasts which differentiate in the usual manner.

It is worth repeating for emphasis that all the foregoing processes may coexist, and that in addition to these types of regeneration, 'blasts and myelocytes which survived the radiation may resume their characteristic functions.

Group 4. Evolution of the newly formed definitive marrow.

The development of the regenerating marrow is so active and so variable that there are no distinct "fixed points" to be seen after the metamorphosis described above has begun. It is desirable to visualize the processes which take place from there on as varying greatly from patient to patient with respect not only to the speed and the quality of the recovery, but also with regard for such complications as blood loss and infection which may also be present. In spite of these qualifications it is possible to classify the recovery phemonena into a series of types. These should not be thought of as necessarily fixed; but should be regarded as points in a continuum at which biopsy examination has been made. The classification of the stages of recovery of marrow and the determination of the time period during which they were generally found should provide a useful guide to the rate of recovery to be anticipated after injury by gamma radiation. The characteristics of the marrow patterns used in this arbitrary classification are listed in Table 17.

TABLE 17

CRITERIA OF TYPES OF REGENERATING MARROW

	CRITERIA
a. Myelocytic:-	Marrow in which the percentage of 'blasts, promyelocytes and neutrophilic myelocytes is the largest portion of all myeloid cells in the differential counts.
b. Metamyelocytic:	Marrow in which the percentage of neutrophilic metamyelocytes is the largest of any type of myeloid cell in the differential count.
c. Left Shift:	Marrow in which the percentage of neutrophilic stab forms is in excess of 25%.

Table 17-continued:

TYPE	CRITERIA
d. Regular:	Marrow in which the relative percentages of each type of myeloid cell approximates the normal values, as listed in Table 1, with due regard for the range of these values as indicated in Table 5.
e. Eosinophilic:	Marrow in which the percentage of eosinophilic leukocytes of all stages is in excess of 8%. In the tabulation of types of marrow (see table 18) the "eosinophilic marrows" are listed without regard to other features.

When the differential counts were studied on this basis, it was found that the marrow biopsy material from Nagasaki displayed a definite trend relating the degree of maturation to the interval of time after exposure to the atomic bomb. The trend is less definite in the material from Hiroshima. These differences appear to be due solely to chance, in the sense that biopsies were performed at more favorable intervals in Nagasaki.

A tabulation of the types of marrow obtained at different times is given in Table 18. Brief discussions and examples of each stage will be presented.

a. "Myelocytic Marrow." Four examples of this type of marrow were seen among the Hiroshima material, 3 early, and 1 late.** There were 10 examples among the Nagasaki material, 2 early in the course of recovery, and 7 later, during the period when hyperplasia was the rule, that is, during October. A typical example is shown in the differential count of the biopsy obtained from Case 3232, 17 October. (See table 19a*)

*See also Nagasaki Cases 404, 409, 3016, 3192, KIU-15, -16, -32, -35 and KUM 87 (See table 11, 19 September)

**See also Hiroshima cases H-6011-U; H-6026-U; H-6031-U; H-6311-P.

TABLE 18

TYPES OF REGENERATING MARROW

HIROSHIMA

Type	Number	1-14 Sept	15-30 Sept	1-15 Oct	16-31 Oct	Nov	Dec
Myelocytic	4	3	-	-	1	-	-
Metamyelocytic	3	3	-	-	-	-	-
Left Shift	31	11	5	7	6	2	-
Regular	19	2	1	2	4	10	-
Total Cases	78	33	11	9	10	15	-
Eosinophilic	3	-	-	-	-	3	-

NAGASAKI

Type	Number	1-14 Sept	15-30 Sept	1-15 Oct	16-31 Oct	Nov	Dec
Myelocytic	10	2	1	1	6	-	-
Metamyelocytic	9	2	2	1	4	-	-
Left Shift	31	-	-	6	15	5	5
Regular	67	-	-	11	35	16	5
Total Cases	178	42	6	24	67	24	15
Eosinophilic	14	1	-	4	7	2	-

(10) Case 3232, Male, Age 62, 1500 meters. (Nagasaki)

Patient was inside a wooden building and sustained mild injuries due to flying debris. There was no epilation, but he suffered from gingivitis from 9 - 13 September. Weakness and progressive debility were the prominent features of the course of the illness. No early laboratory data were available.

Examination of the blood.

DATE	Hb.	RBC	WBC	PROTEIN
12 Oct.	35%	2.02	4,650	6.5
29 Oct.	40%	2.25	5,100	
7 Nov.	45%	2.37	6,680	6.7
13 Nov.	35%	1.91	5,550	5.5

Other laboratory data: Reticulocytes, 20 October: 0.4%

Platelets, 16 October: 131,000

Differential Counts:

DATE	POLYS	LYMPHS	MONOS.	EOS.	BAS.
12 Oct.	74	9	2	14	1
13 Nov.	72	19	3	4	2

A typical field from a smear of "myelocytic marrow" is shown in Figure 39. The smear is from a biopsy of KUM 87, obtained 19 September. (See table 11, (1) Case, Page 27

b. "Metamyelocytic Marrow." There were 3 examples of this pattern among the Hiroshima material, 2 of which were obtained early in September. The Nagasaki specimens included 9 of this type, the majority collected during the period 15 September-31 October. A typical example is seen in the differential count, (see table 19b) of the marrow obtained from Case H-6033-U, 7 September.*

(11). Case H-6033-U Female. Age 24. 1800 meters. (Hiroshima.)

Patient sustained contusions at the time of the bombing. Epilation did not occur, but pharyngitis and stomatitis, which became ulcerative, appeared on 31 August. Purpura was observed first on 2 September. The patient had a protracted febrile course, but ultimately recovered.

Examination of the Blood.

DATE	Hb.	RBC	WBC
6 September	45%	2.46	1,100

Differential Count:

DATE	POLYS	LYMPHS	STAB FORM	NUCLEATED RED CELLS
6 September	12%	74%	12%	2%

c. "Left Shift Marrow": 31 examples of this pattern of marrow were obtained in the material from each city. The tendency was noted for this type of marrow to develop mainly during October or later. A conspicuous example has already been cited, Case H-6025-U. (See table 14 and (7) Case,) where a left shift was found not only in early marrow, obtained 6 September, but also in a later specimen of 12 November. A biopsy performed on 27 September, however, was found to have the characteristics of a "regular marrow". Another example is Case 314 (Nagasaki), the differential marrow count for which is shown in Table 19c.

*See also Hiroshima Cases 0-12161-Osaka and Nagasaki Cases 3093, 3192, KIU-17, 18, 23, 25, 30, 31 and 33.

TABLE 19

EXAMPLES OF DIFFERENTIAL COUNTS OF STERNAL MARROW

	A	B	C
Case No.	3232 "MYELOCYTIC"	H-6033-U "METAMYELOCYTIC"	314 "LEFT SHIFT"
Blast	0.9	-	0.5
Promyelocyte	1.5	1.0	1.0
Myelocyte	15.5	15.5	14.5
Metamyelocytes	13.5	18.0	7.5
Stab Form	16.5	16.0	34.0
Poly	9.5	7.0	4.5
Eosinophile(all)	6.5	3.5	5.5
Lymphocyte	4.0	12.0	10.5
Monocyte	1.5	1.5	1.0
Histiocyte	0.4	0.5	-
Plasma Cell	2.0	3.5	3.0
Erythroblast	7.4	2.0	6.0
Normoblast	20.5	15.5	12.0
TOTAL NUCLEATED CELL COUNT	-	8600	-
Date	17 October	7 September	20 October

(12) Case 314: Male. Age 18. 1600 meters. (Nagasaki)

Patient was inside a thin sheet-metal building, and sustained moderate flash burns of face and hands. Epilation occurred about 7 days after the bombing and pharyngitis developed early in September. The burns healed well, but recovery from the radiation injury was protracted.

Examination of Blood:

DATE	Hb	WBC	PROTEIN
2 October	75%		
10 October	73%	13,800	7.5
2 November	68%	7,850	7.8

Differential Counts:

DATE	STABS	POLYS	LYMPHS	MONOS.	EOS.	BAS
10 October	*	29	51	1	6	1
2 November	8	27	40	9	15	*

d. "Regular Marrows" were observed quite frequently in the material obtained from the recovering patients. It will be seen from Table 18 that this is a late development, as would be expected, and that the majority of specimens displaying this pattern were collected after 16 October, in each city. As a result of grouping the types of marrow as observed on smears in this manner, several features of the process of regeneration are apparent. (See table 18.) First, it is not surprising to find that recovery is correlated with a progressive "shift to the right" of the myelograms of patients who survived. Second, the time relations of the several stages of evolution display considerable variation from case to case. This variability is a complex result of

* 1 Metamyelocyte was noted.

the two major imponderables: the radiosensitivity of the individual; and the actual dosage of gamma rays. If the number of biopsy specimens were greater it should be possible by grouping patients with respect to their distance from the bomb, to elucidate this point further. Since this is not feasible, there is no reason to pursue this phase of the subject at greater length.

e. "Eosinophilic Marrow". Eosinophilia was observed much more frequently in the marrow of patients from Nagasaki than in the Hiroshima group. This discrepancy is undoubtedly due to chance in the sense that more biopsies were performed at an appropriate time in the former city. The actual incidence was 3 of 78 cases for Hiroshima, and 14 of 178 cases for Nagasaki, respectively. The distribution of the latter cases on a time basis is shown in Table 18. Figure 44 shows the appearance of marrow tissue obtained at autopsy from one such case, Shinkozen 4-318 (Nagasaki), Key #194. A brief review of the clinical record discloses the following:

(13) Case, 318, Male, Age 8. 700 meters. (Nagasaki).

Patient was inside a wooden building, and received multiple lacerations due to glass fragments as well as severe radiation injury. He was cared for in the Shinkozen Medical Aid Hospital and no early records of laboratory studies were found. Epilation of the scalp had occurred, but no other symptoms attributable to radiation injury were noted. He contracted lobar pneumonia and died 4 October. The discrepancy between the eosinophilia of the marrow and the lack of it in the peripheral blood is interesting

Examination of Blood.

DATE	Hb	RBC	WBC
4 October	58%	2.37	27,600

Differential Count.

DATE	STABS	POLYS	LYMPHS	MONOS
4 October	15	78	5	2

The average marrow eosinophile percentage in each time period for Nagasaki cases is shown in Table 20. It will be seen that average values show a trend with the maximum in October; but at this time the mean is not greatly in excess of average normals. The high value for December should be ignored because of the small number of cases. For normal values refer to Table 1 where the averages in two series of Japanese subjects were 4.2% and 4.3% respectively. A further analysis of the Nagasaki patients with "eosinophilic marrow" shows that their distribution with respect to distance from the bomb was quite similar to that of the entire group. (See table 21).

TABLE 20

AVERAGE PERCENTAGE OF ALL EOSINOPHILIC CELLS IN MARROW (NAGASAKI CASES)

MEAN PER CENT EOSINOPHILES	TIME PERIOD	TOTAL NUMBER OF CASES
2.9	1-14 September	42
2.1	15-30 September	6
5.5	1-15 October	24
4.9	November	24
6.5	December	15
4.2- 4.3	Normal	

TABLE 21

DISTANCE FROM BOMB

All Nagasaki Cases with Marrow Biopsy (Table 3)	Meters	Cases with Eosinophilic Marrow
6	0 - 500	1
23	600 - 1000	4
57	1100 - 1500	7
21	1600 - 2000	2
13	Beyond 2100	0

The data in Table 21 suggest that the eosinophilic group is representative and that the finding is probably not to be attributed to some extraneous factor, as say parasitic infestation. Some of the Japanese workers reported that blood and marrow eosinophilia was a favorable prognostic sign (Appendix 4N - 25); but the total number of cases on which this conclusion was based was too few to justify it. In attempting to assess the significance of these changes it may be recalled that blood eosinophilia has been described as a typical sequel of roentgentherapy (Minot and Spurling, 1924, loc. cit.). The maximum values observed by radiologists is of the order of 25% which is considerably less than the maximum of 68% eosinophils found in the blood of case #3122. (See Table 22a)

(14) Case 3122, Female, Age 25, 1700 meters, Nagasaki.

Patient was inside a wooden building and sustained many lacerations due to flying fragments of glass, as well as radiation injury. Epilation appeared early, and purpura and gingivitis were evident during the 1st week of September. Hemorrhagic retinitis associated with amblyopia was still to be seen in October. The course of recovery was slow.

Examination of Blood.

DATE	HB	RBC	WBC	PROTEIN
20 September	-	-	2500	-
2 October	52%	-	16450	8.5
16 October	43%	-	8500	7.8
26 October	60%	-	16200	8.4
13 November	48%	-	11050	7.8

Differential Counts

DATE	POLYS	LYMPHS	MONOS	EOS.	BAS
2 October	29	8	6	61	1
16 "	14	15	7	64	-
26 "	11	17	4	68	-
13 November	43	24	2	31	-

b. Erythropoiesis: The manner in which the erythropoietic function of bone marrow recovers after exposure to injurious doses of gamma radiation is not too clear. It has been demonstrated in the early period after irradiation, while the proliferation of reticulum is the main process to be seen, that a certain number of nucleated red cells, chiefly normoblasts, can be found. It was suggested that these were probably cells that had survived amounts of radiation which had apparently destroyed all, or nearly all the myelopoietic tissue. A study of the specimens with particular regard for the metamorphosis of reticulo-endothelium into erythropoietic cells has provided several examples of this process. The type of reticulum cell which is involved does not appear to differ in any important respect from the type which differentiates into a granulopoietic cell. No azurophile granules develop however, and the cytoplasm tends to become increasingly basophilic, and in most instances loses the flocculent, or ground-glass texture which is characteristic. The changes in the nucleus are also distinctive when the apparent metamorphosis is in the direction of the red cell series. The chromatin becomes more dense, and the threads of it become compacted together. The conspicuous nucleoli of the reticulum cell become less distinct, and fewer of them can be seen. At about this stage the cell is readily identifiable as a very immature basophilic erythroblast (pronormoblast, proerythroblast). From this stage on, there appears to be nothing abnormal in the evolution of the adult erythrocytes. An example of this type of early red cell development is shown in Figure 45.

The specimen is a biopsy, H-11879-KPS, obtained 12 September. Another example showing the contrast between the early erythroblast and the equivalent cell of the myeloid series is seen in Figure 46, which is also from a biopsy, H-6016-U, performed 6 September. This patient is (5) Case, Page 30. The further development of erythropoiesis is shown in the series, Figures 47, 48, and 49. In the last figure a nest of polychrome normoblasts of quite normal appearance is shown. These illustrations are all taken from a biopsy, H-10335-U, performed 24 September. (See table 22c) There is no way that is readily apparent to distinguish basophilic erythroblasts recently metamorphosed from reticulum. from ordinary erythroblasts which can be presumed to have survived the gamma radiation.

Many of the biopsy specimens impress the examiner as resembling foetal erythropoieis in the sense that there appears to be a larger proportion of polychrome normoblasts and polychromatophilic erythrocytes than is usual in adult marrow. The data unfortunately has not been collected in a manner which

TABLE 22

EXAMPLES OF DIFFERENTIAL COUNTS OF STERNAL MARROW

	A 3122 "EOSINOPHILIC"	B 3069 ACTIVE ERYTHROPOIESIS	C H-10335-U VERY ACTIVE ERYTHROPOIESIS
'Blast	-	2.0	-
Promyelocyte	2.7	2.0	1.5
Metamyelocyte	7.7	8.5	7.0
Stab Form	15.4	24.0	25.0
Poly	4.4	10.5	8.5
Eosinophile-all types	41.8	3.0	2.0
Lymphocyte	2.7	4.0	5.0
Monocyte	0.5	2.5	1.5
Histiocyte	-	0.5	0.5
Plasma Cell	1.1	-	0.5
Erythroblast	4.0	4.5	4.5
Normoblast	14.3	32.0	41.5
	17 October	13 October	24 September

67 (7)

will permit substantiation of this observation. It has been shown, however, in the section on the Blood (Section 6) that the number of reticulocytes in peripheral blood was never very great in the recovering subjects. There is apparently a discrepancy here between the obvious immaturity of the erythrogenic marrow and degree of reticulocytosis in the blood. This has been noted by all who have examined the material, but there is no easy explanation of the finding.

It was shown in Table 9 that the myeloid: erythroid ratio calculated from differential counts of sternal marrow was the lowest during the period 16-31 October. Since this period was also the time at which the average value for the total nucleated cell count in marrow was the greatest, it is proper to assume that erythropoietic regeneration was maximal at this time, on an average. The data was reviewed to determine the incidence and the time relation of examples of especially marked regeneration of the erythrogenic function. For this purpose two categories were selected arbitrarily:

a) Active Erythropoiesis: Instances where the total percentage of nucleated red cells was between 30% and 40%, inclusive.

b) Very Active Erythropoiesis: Instances where the total percentage of nucleated red cells was in excess of 40%.

The results of the analysis are shown in Table 23 and typical examples of the differential count of a case in each category is listed in Tables 22B and 22C, respectively. Brief clinical data on these patients are presented.

TABLE 23

INCIDENCE OF UNUSUAL DEGREES OF ERYTHROPOIESIS

HIROSHIMA					TYPE	NAGASAKI					
1-14 Sept.	15-30 Sept.	1-15 Oct.	15-30 Oct.	Nov.		1-14 Sept.	15-30 Sept.	1-15 Oct.	16-31 Oct.	Nov.	Dec.
2	-	2	4	2	Active erythropoiesis	24	-	-	7	5	2
2	1	-	-	3	Very active erythropoiesis	10	-	-	2	8	-
33	11	9	10	15	All Types	42	6	24	67	24	15

(15) Case 3069. Male. Age 22. 550 meters. (Nagasaki)

Patient was inside a wooden factory building, and received very many lacerations of the entire body due to glass fragments. Epilation commenced 19 August; and gigivitis with some purpuric tendency developed early in September. The course of recovery was very slow and his general status in November was still not good.

Examination of blood:

DATE	Hb.	RBC	WBC	Protein
26 August	43%	3.48	2200	-
25 Sept.	33%	1.90	3000	-
6 Oct.	58%	-	10450	6.8
25 Oct.	82%	-	7400	-
13 Nov.	78%	-	2450	7.0

Differential Counts:

Date	POLYS	LYMPHS	MONOS	EOS	BAS
6 October	71	26	2	1	-
25 Oct.	63	25	8	4	-
13 Nov.	16	58	8	17	1

Additional Laboratory Data:

Reticulocytes, 22 October - 0.4%

Platelets 23 October - 158,000

This record is quite interesting because of the poor reticulocytosis at a time (mid-October) when the marrow contained many normoblasts. The recurrence of leukopenia is curious, and not easily explained with the material available. See Table 22 B

(16) Case H-10335-U Male. Age 23. 1000 meters. (Hiroshima) Table 22 C

Patient was sitting inside a wooden building, but received no injury except by radiation. Purpura, stomatitis and ulcerative pharyngitis occurred about 1 September. Epilation was not observed until 15 September. He was hospitalized and was thought to have typhoid fever in addition to the radiation sickness. He recovered and left the hospital 7 October. (See figures 47, 48, 49)

Examination of Blood:

DATE	Hb	RBC	WBC	RETICULOCYTES
19 September	39%	1.57	4500	-
24 September	39%	2.04	5200	6.9%

Differential Counts:

	19 September	24 September
Metamyelocyte	0.5	1.5
Stab Form	23.5	13.5
Poly	29.5	64.0
Lymphocyte	21.0	13.5
Monocyte	13.5	7.0

Differential Counts-continued:

	19 September	24 September
Eosinophil	0.5	- -
Basophil	-	0.5
Plasma Cell	-	1.0

From this cursory review of the recovery of erythropoiesis it is evident that the same processes operate as in the case of the granulocytic cells. There is considerable clinical evidence for defective evolution of this function, as represented by cases where the clinical syndrome of hypoplastic anemia persisted or gradually became worse, 12-14 weeks after irradiation. There is, however, no characteristic feature of the marrow specimens from such cases. A typical example of this late deficiency is Case 10. (Key #190)

(17) Case #10. Male. Age 58. 1300 meters. (Nagasaki).

Patient was standing in the open, and sustained extensive second degree burns of exposed portions of the body, as well as of parts covered by clothing. Epilation commenced at an unspecified time, but no other symptoms of radiation injury were recorded. The burns were healed satisfactorily by the 1st of October, but his general condition deteriorated steadily. A diarrhea commenced 11 October and persisted until death, apparently from cachexia, on 18 November.

Examination of Blood:

DATE	Hb	RBC	WBC	PROTEIN
5 October	72%	2.00	5350	5.4
1 November	51%	3.10	4550	4.5
18 November	18%	0.85	1600	4.5

Differential Counts:

DATE	POLYS	LYMPHS	MONOS.	EOS.
5 October	78	12	7	3
1 November	78	18	2	2

Reticulocyte Count: 1 November. 1.8%

Stool cultures were reported as negative for pathogens. The low power view of the marrow (See figure 50) shows a fairly cellular tissue, but more careful inspection reveals no polys or other adult cell types.

In the past there has been considerable speculation as to which group of human marrow cells, the red or the white, is more radiosensitive. The present data has been examined carefully with this question in mind, but allowing for differences in the tempo of the reactions in each system, it is not possible to produce a defensible answer at the present time. It is apparent that the granulocytes are destroyed promptly and that at a time when all these are absent, a few normoblasts remain. It has been suggested that these latter are survivors, but since they are relatively mature types which would shortly develop into the comparatively radio-insensitive erythrocytes, it does not seem proper to appraise the sensitivity of the erythropoietic system on the basis of them. The burden of the evidence indicates that the white cell forming tissue recovers sooner than the erythrogenic structures. There is no more reason to attribute this to differences in radio-sensitivity than there is to explain it by differences in rate of growth of the two tissues. Clinical examples were observed where it appeared that the erythropoietic function had recovered more completely than the myelopoietic one, and vice versa.

In view of the ambiguous nature of the evidence cited, it is well to reserve judgment. Perhaps, long range observation of recovered patients will provide a more satisfactory answer.

C. Megakaryocytes. The smears of aspirated marrow obtained early in the course of the syndrome of radiation injury rarely contained appreciable numbers of megakaryocytes. As a matter of fact, the ordinary technics for bone marrow biopsy provide indifferent information about the relative numbers of these large, fixed cells. For this reason, the percentage of megakaryocytes is not included in the tabulation of the differential cell count. In the tissues obtained at autopsy, these cells may be studied more readily, and it was found that their behavior roughly paralleled the changes in the myelopoietic tissues. There appears to be a fair correlation between the time period when the platelets were least numerous (see section on Blood) and the period when the fewest megakaryocytes were seen in the marrow (see section on Pathology). The development of megakaryocytes from reticulum has been described in various blood dyscrasias and in experimental animals, and instances were observed in the irradiated patients which demonstrated this process. Specific examples are shown in the Pathology section.

Group 5. Unsatisfactory evolution of the "reticular marrow".

It is reasonable to anticipate that the marrow will not regenerate in a satisfactory manner in some cases. Since this type of failure should facilitate the death of the subject, the autopsy material has been studied with particular regard for evidence of abnormal patterns of regeneration. A tentative classification of the conditions of unsuccessful recovery of marrow is as follows:

1) Failure of the reticulo-endothelium to proliferate, sufficiently, with the result that substantial numbers of definitive cells are produced.

2) Failure of the metamorphosis of an "adequate", or abundant reticular

marrow to occur rapidly or completely enough to provide sufficient adult granulocytes and erythrocytes.

3) Abnormal evolution (or differentiation) of the reticulo-endothelium with the production of substantial numbers of cells of other varieties than adult granulocytes and erythrocytes.

The first two conditions are rather obvious eventualities and it is possible to interpret many of the biopsy and autopsy specimens in such a manner. The third condition is the subject of discussion in the present section.

It is evident that the development from the reticulo-endothelium of cells other than the highly desirable granulocytes and erythrocytes may vary greatly both as to kind and as to extent. Thus, it may be expected that cases will be found where the number of abnormal cells will be few or many, or where their site of development will be focalized or generalized. It has been shown that in the early period of recovery, after exposure to the atomic bomb, the proliferation of reticulum is associated with, and is probably the source of, plasma cells, macrophages, and abnormal lymphocytes. Later it appears that the reticulum produces fewer of these cells and undergoes a metamorphosis into a tissue consisting of definitive myelopoietic and erythropoietic cells. It is reasonable, therefore, to expect that certain instances will be found where the early type of differentiation has persisted, or has become, or remained the dominant activity.

Plasma cells were seen in large numbers in specimens obtained at autopsy and biopsy during the first 3-5 weeks after irradiation. In some instances, 30% to 40% of the nucleated cells in marrow were of this type. Plasma cells are still to be seen but in decreasing numbers in all the specimens obtained late (i.e. last half of September, October, November, December) after injury, There was no example found during this period where the number of plasma cells or their distribution was such as to suggest that they were proliferating in an abnormal manner nor was there any example of tissue which resembled multiple myeloma. The same can be said in general, for macrophages; and there were no "late" cases where unusual numbers of these cells were observed.

In the marrow obtained by puncture biopsy, appreciable numbers of abnormal lymphocytes were found on many occasions. In Table 16, page 48 it was shown that the incidence of this type of cell in significant numbers (i.e. more than 1% of all the cells counted) was 56% for Hiroshima, and 31% for Nagasaki cases, respectively. It was also shown that these forms could be found at any time after the bombing when the marrow was examined. In fact, about one-half of all the specimens obtained in November in each city, and in December in Nagasaki, contained some abnormal lymphocytes. The significance of the persistence of abnormal lymphocytes is difficult to assess. One point of view may be that since the marrow continues to produce this type of cell, therefore the process of metamorphosis of the reticulum is incomplete. Another view may be that the response of the reticulum to infection, etc., is altered and the abnormal lymphocyte may continue to be one of the characteristic products of "irritated" reticulum in such subjects. There is, however, insufficient data available to establish either point of view satisfactorily. There is, also, inadequate data to permit the establishment of limits of "normality" for the occurrence of these cells. It must be sufficient to state here that lymphocytes of this type are seldom encountered in bone marrow under any conditions and that the high rate of occurrence of them in these specimens is thus of some interest. Since it is not possible to interpret the finding, a group of cases will be presented simply to demonstrate the appearance of such cells late in the course of the syndrome of radiation injury.

(18) Case 410. Female. Age 33. 1300 meters. (Nagasaki)

Patient was inside a wooden building, and sustained minor flash burns of the face and arm, as well as minor injuries due to flying debris. Gingivitis and pharyngitis occurred late in August, and epilation and purpura commenced in September. Amenorrhea persisted from the time of the bombing. The wounds and burns healed satisfactorily and she made a slow recovery from the effects of the radiation.

Examination of blood:

DATE	HB	RBC	WBC	PROTEIN
5 October	63%	3.10	7050	6.5
19 "	70%	3.00	9850	6.7
7 November	72%	-	6500	6.7
15 "	82%	-	5400	7.0
16 "	61%	4.69	7000	-

Figure 41 is a representative field from a smear of marrow obtained by biopsy on 16 December, and shows the presence of the large abnormal lymphocyte. There are also myelocytes to be seen with the deficient type of granulation associated with the metamorphosis of abnormal lymphocytes into granulocytes.

(19) Case H-10616-I Female 19 200 meters (Hiroshima)

Patient was inside on the first floor of a 3 story concrete building. She received minor wounds and radiation injury. Epilation occurred early in September. There were no other symptoms, and she recovered and appeared well in November, 16 weeks after the bombing.

Examination of Blood:

DATE	Hb	RBC	WBC
13 August	48%	2.35	3400
15 "	45%	2.34	1340
16 "	43%	2.20	1250
18 "	40%	2.15	2480
20 September	-	-	-
19 November	78%	3.87	4500

Differential Count:

DATE	STAB	POLYS	LYMPHS	MONOS	EOS	BAS	PLATE-LETS
19 November	8.0	54.4	27.2	4.0	4.0	4.0	65790

Figure 51 is a typical field from a bone marrow biopsy performed 19 November. The large number of abnormal lymphocytes, as well as what appear to be cells transitional between the reticulum cell and the lymphoid cell, are shown. This specimen is very interesting, for the patient is one of the few survivors of the group who were irradiated in the Banker's Club. (See Section 11 H)

A striking example of the persistence of abnormal lymphocytes is seen in Key #50, died 15 November 1945. This patient, H-6059-U, was inside a wooden building at 1000 meters, in Hiroshima. He survived a severe illness due to radiation injury, with epilation, purpura and oropharyngeal ulceration, and finally died from bronchiectasis. Imprint preparations of marrow, made post mortem contained numerous abnormal lymphocytes, many of which can be seen to be in the process of developing specific granulation. In Figures 52, 53, 54, 55 this process is shown and in many instances it is impossible to decide whether the cell is a lymphocyte or a myelocyte. In the photomicrograph of the tissue, Figure 56, the intermediate and indeterminate character of the nuclei of these cells is shown. A sternal biopsy was performed on this patient 17 October, and although abnormal lymphocytes are to be seen, the process which is pictured here was less obvious at that time.

Other examples of the persistence of appreciable numbers of abnormal lymphocytes in marrow are shown in Figures 57 and 58, from Case S-9078-KO of 5 November and Figure 59, from Case H-6052-U of 29 October. In contrast to these subjects in whose marrow abnormal lymphocytes were conspicuous, attention is invited to Figures 60 and 61 from Case H-6729-U of 24 October. The differential count of this smear disclosed that 50% of the nucleated cells were quite ordinary small lymphocytes, of normal appearance. The only common feature of these six patients is their injury by gamma irradiation. It is apparent that further study is necessary before the significance of the persistence of the abnormal lymphocytes can be interpreted justly.

The failure of the reticulum which has proliferated to complete its metamorphosis into a "definitive" marrow may occur in such a way that a marrow is formed which contains large numbers of these cells, and their early derivatives, but little evidence of the maturation of these latter types. The inefficiency of such a tissue is obvious, and the failure of myelocytes which have developed from the reticulum to undergo orderly maturation is interesting, but it may be presumed that the desirable situation would be for ordinary 'blasts to form from the reticulum in suitable numbers. These 'blasts could then, in turn, produce granulocytes in the normal manner. Two excellent examples of the failure of the metamorphosis of reticulum into normal myelopoietic tissue are available, and since the changes in the histological preparations are supported by good smears of marrow, they will be presented here.

(20) Case 3098, Female, 60, 800 meters, Nagasaki.

Patient was outdoors, prone, and unshielded. She sustained severe 2nd degree burns of the posterior aspect of her body. The burns of the legs became infected and contractures developed. She had no epilation, but noticed purpura at an unspecified time. Her course was unsatisfactory and progressive cachexia occurred. She died 15 October.

Examination of Blood:	Date	Hb	Rbc	Wbc
	5 Sept	-	-	3200
	8 Oct	52%	2.17	8550

Differential Count:

8 Sept: Stabs - 6; Polys - 37; Lymphs - 39; Monos - 4; Eos - 14

The sternal marrow was hyperplastic at autopsy, and proliferation of reticulum was evident. The majority of the cells to be seen were mononuclears, some of which were lymphocytes, plasma cells, reticulum cells and myelocytes. In the smear the identity of the majority of the cells was apparent (See Figure 62). Typical large, rounded-up reticulum cells were numerous; and many contained a varying amount of azurophile granulation. Some of these also had neutrophilic granulation in small amounts. These were considered to be early forms of abnormal myelocytes, and these were the most numerous type of cell. Metamyelocytes, stabs, and polys were scarce. A number of basophilic erythroblasts were present, but maturation of this series was also defective. The general character of the cytological processes resembled that seen in the 'early' stage in most of the severely affected patients. The persistence into the 10th week of a stage which ordinarily occurred in the 3rd to 5th week is extremely interesting.

(21) Case 3121, Male, 65, 900 meters, Nagasaki

Patient was standing outdoors behind a tree and received no injury except by radiation. There was no epilation, but gingivitis and purpura commenced early in September. He developed gradually after the bombing a generalized dirty brownish pigmentation which resembled that seen after roentgentherapy. He left the hospital without permission 9 October and thus was not worked up by the doctors of the Joint Commission. He returned in a moribund state, 11 November, and died the same day. The only clinical information obtained was that he had continued to have diarrhea after leaving the hospital and had become progressively weaker without any definite complaints.

Examination of Blood:

DATE	RBC	WBC
27 September	4.16	4400

The sternal marrow was fairly cellular at autopsy, and contained a moderate amount of erythropoietic tissue, but the predominant type of cell was a reticulum-like mononuclear. Imprint preparation (See figure 63) contained many typical, large rounded-up reticulum cells, only a portion of which contained azurophile granulation. A small number of myelocytes of the type formed from reticulum were seen; and metamyelocytes and stab forms and polys were very few in number. Plasma cells and lymphocytes were numerous. The general appearance of this marrow obtained in the 14th week after bombing was similar to that from severe cases who died in the 3rd-4th weeks.

These two cases (20) and (21) illustrate quite well the persistence of the proliferation of reticulum which is undergoing metamorphosis into myelocytes. However, the latter cell types do not appear to be maturing in the usual manner, and there is very little evidence of the differentiation of the reticulum or its product into even small amounts of normal marrow tissue. There is no evidence that can be recognized to explain the reason for the failure of ordinary myeloid tissue to form, nor is there any indication as to why this early pattern of regenerating marrow continued for so long a period.

On the basis of the known action of ionizing radiations on biological material, it is reasonable to anticipate that some instances might be found where leukemic, or pre-leukemic changes could be recognized in the marrow and the lymphoid structures. Experimentally leukemia has been produced in animals, particularly mice, by exposure to varying amounts of roentgen rays. The factors of duration of exposure and intensity of radiation necessary to provoke the development of leukemia are not thoroughly known. It has been shown, however, by Furth (1) and also by Boehe (2) that single large doses may be as effective in causing leukemia as repeated small exposures. The ability of the human species to develop leukemia as a consequence of roentgen irradiation is indicated by the high incidence of the disease in radiologists. (1). In none of the marrow biopsy specimens obtained in either city was there any evidence to suggest that leukemia was developing. The most persistently abnormal marrows from the cytologic standpoint have been mentioned in preceding sections; but there is no reason to describe any of them as leukemia or even as pre-leukemia. Among the autopsy specimens there were several cases where the proliferation of the reticulum in the marrow and in the lymphoid organs was especially pronounced. The marrow of these cases displayed little evidence of orderly metamorphosis of the reticulum. The cases are described in detail in the section on Pathology. They are not examples of leukemia, but the poor differentiation of reticulum which is seen bears some resemblance to the processes observed in irradiated animals, which have developed leukemia.

One case of "Monocytic leukemia" occurred in a medical student who had recovered from a severe form of the syndrome of radiation injury. It is described in detail in the Pathology section. This patient experienced a period of good health of some 5-6 weeks duration between the time of recovery from the effects of severe radiation sickness and the onset of the symptoms of acute leukemia. Because of reasonable doubt as to the role of the gamma radiation in the genesis of the leukemia, no further comment is appropriate.

(1) Furth, J. "Recent Experimental Studies on Leukemia", Physiol. Rev. 26: 47-76, January 1946.

(2) Boehe, Personal communication. Data to be published.

SUMMARY

A study of the specimens of bone marrow obtained by biopsy and at autopsy revealed the following features of the reaction of human hematopoietic tissue to lethal and sublethal doses of ionizing radiation.

1. The marrow was seriously affected by the gamma radiation of the atomic bomb. The definitive cells were markedly reduced in number or were entirely destroyed. The period of maximum depletion of these cells appeared to vary from patient to patient, but occurred in general between the 6th and perhaps the 30th day after exposure.

2. In almost every patient who survived longer than 6 days after irradiation, there was evidence of the proliferation of the reticulo-endothelium.

3. At first, the only products of this proliferation were reticulum cells, macrophages, plasma cells and lymphocytes.

4. After a period of time, which varied from 1 to 3 weeks, the reticulum cell underwent a metamorphosis resulting in the development of definitive granulocytogenic and erythrogenic tissue.

5. There was evidence for the transformation into myelocytes of the abnormal lymphocytes which developed from the reticulo-endothelium, and there was reason to believe that these myelocytes could maturate into polymorphonuclear leukocytes.

6. There was evidence for the regeneration of both red and white marrow from 'blasts of the appropriate type which survived the gamma irradiation.

7. There appeared to be three means by which marrow damaged by ionizing radiation regenerated. These are summarized in 4, 5) and 6) above. It is very probable that any or all of these methods may be operative in a given case.

8. As regeneration progressed, there was a steady "shift to the right" of the myeloid tissue, beginning from a very immature "reticular" or "myelocytic" marrow, and ending in favorable cases, with one that closely approximated the normal.

9. The time required for the myelopoietic tissue to recover completely varied among patients, but in most instances, when it occurred, restitution to a normal status was seen by the 12th to 16th week after exposure.

10. The recovery of the erythropoietic portions of the marrow appeared to proceed at a slower rate than granulopoiesis, but each system appeared to reach a normal state at about the same period of time.

11. The cellularity of irradiated bone marrow is not certainly known at all stages, but it was found to be reduced to less than 10% of normal in the 3rd to 5th week after exposure. The maximum cellularity of the average regenerating marrow was about 50% greater than normal and was found during the 10th-12th week after irradiation.

12. The tendency of the marrow to recover promptly after large doses of gamma irradiation to the whole body is an important fact. The ability of the reticulo-endothelium to participate in, and possibly to effectuate this recovery after irradiation is a significant physiological finding.

13. The process of regeneration failed or occurred in an unsatisfactory manner in some patients. In some instances there was evidence that the proliferating reticulo-endothelium failed to differentiate into adequate numbers of definitive cells. In other instances young definitive cells developed, but failed to undergo maturation into adult forms. In still other instances, the marrow appeared to contain normally matured cells which failed to gain access to the circulating blood in adequate numbers.

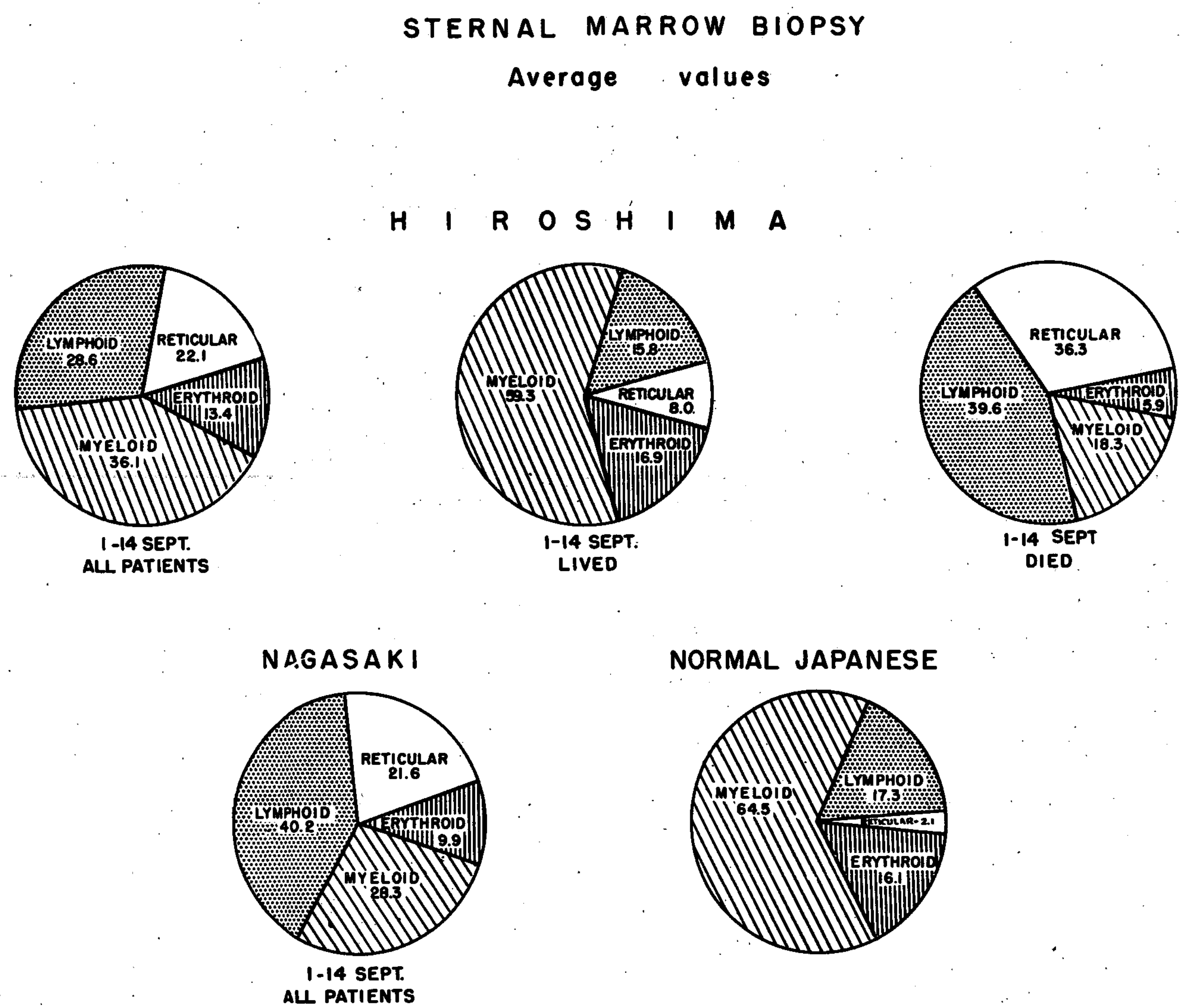


Fig. 1 (7)--Pie diagrams of sternal marrow differential count. The class "reticular" includes monocytes, histiocytes, macrophages, plasma cells. Where the total count of nuclear marrow cells is known it appears directly above the "pie" concerned. (Photo File # HM 292.)

STERNAL MARROW BIOPSY
Average values

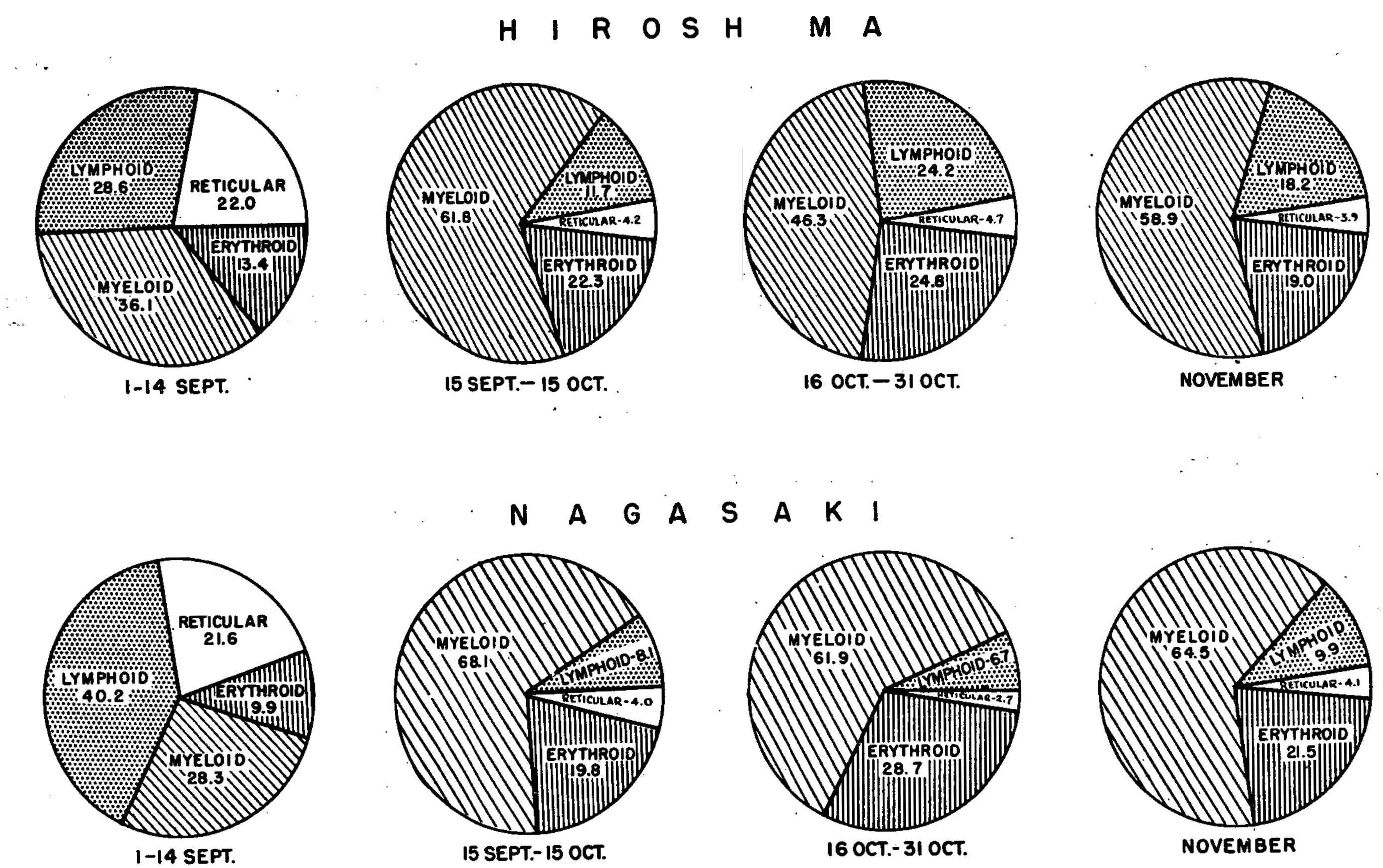
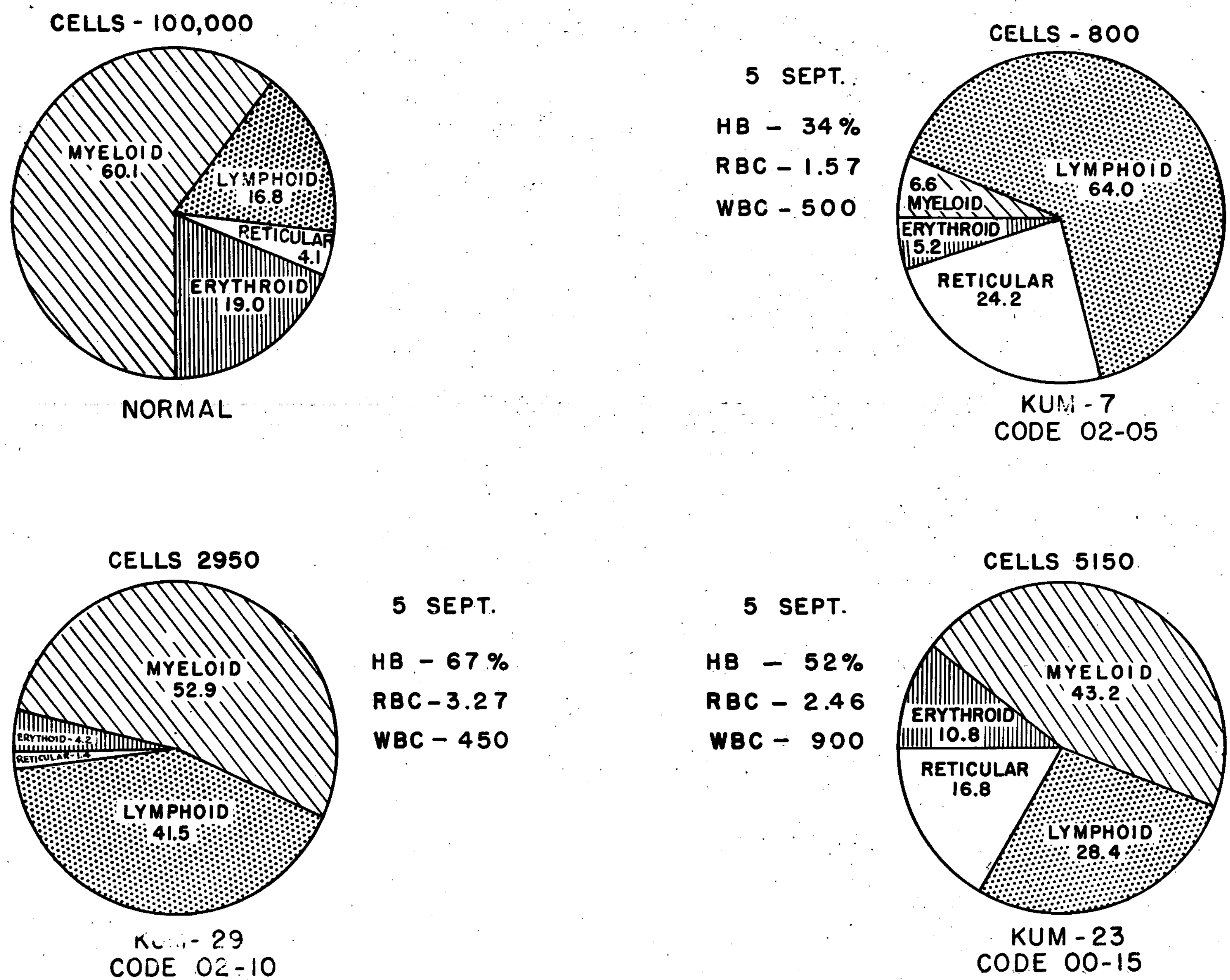


Fig. 2 (7)--(Photo File # HM 291)



STERNAL MARROW BIOPSY

Fig. 3 (7)--(Photo File # NM 146.)

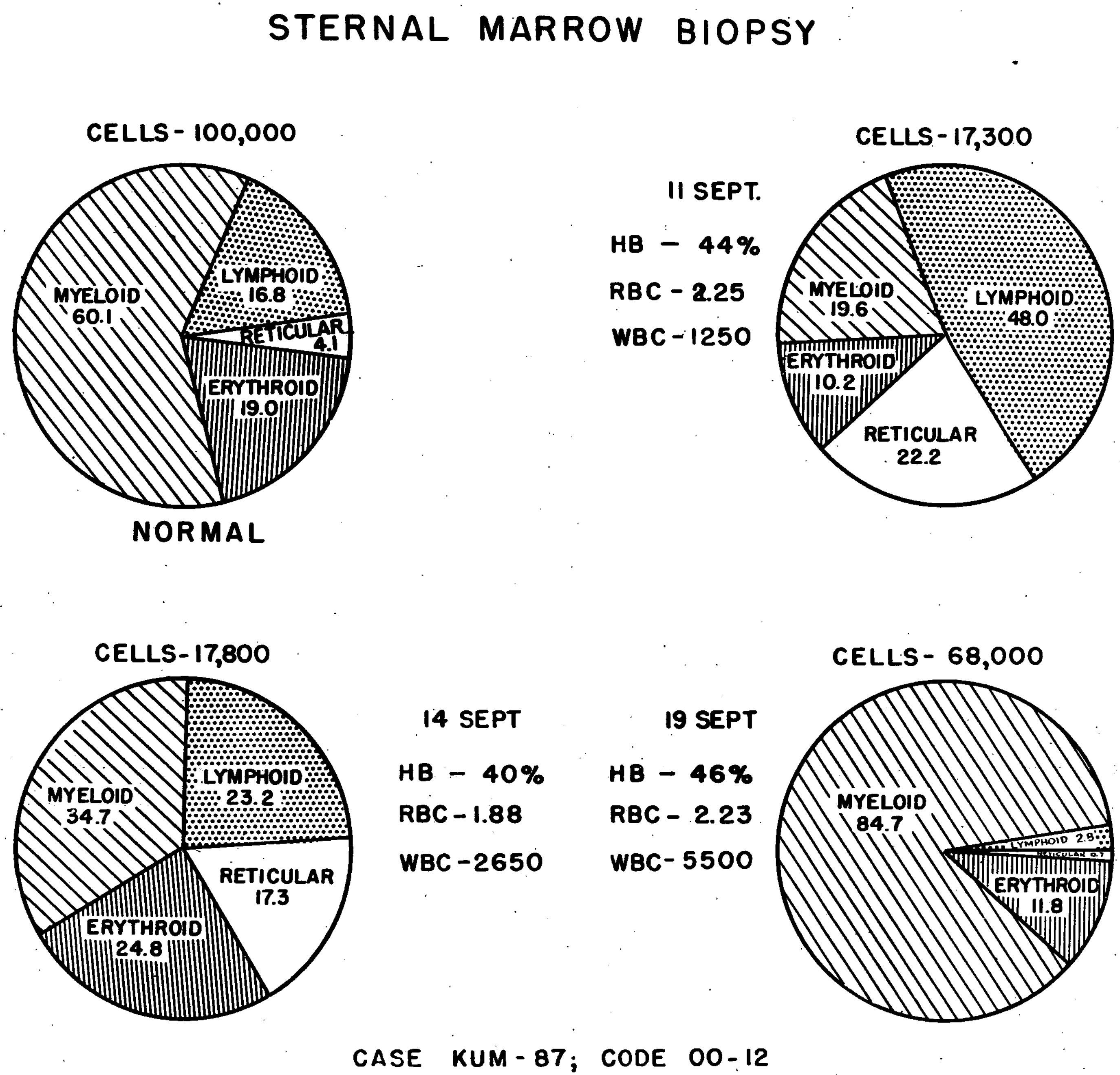


Fig. 4 (7)--(Photo File # NM 145.)

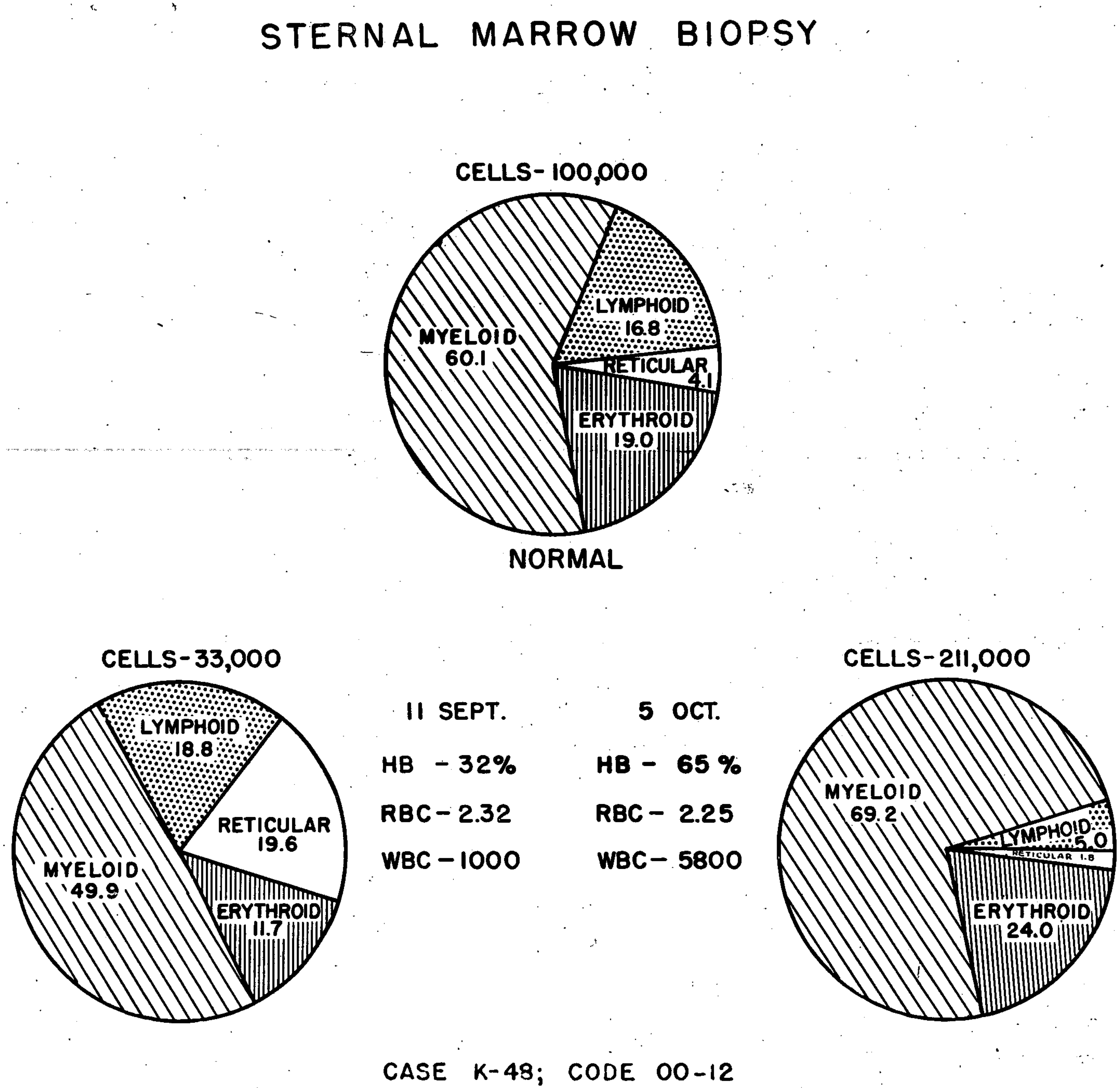
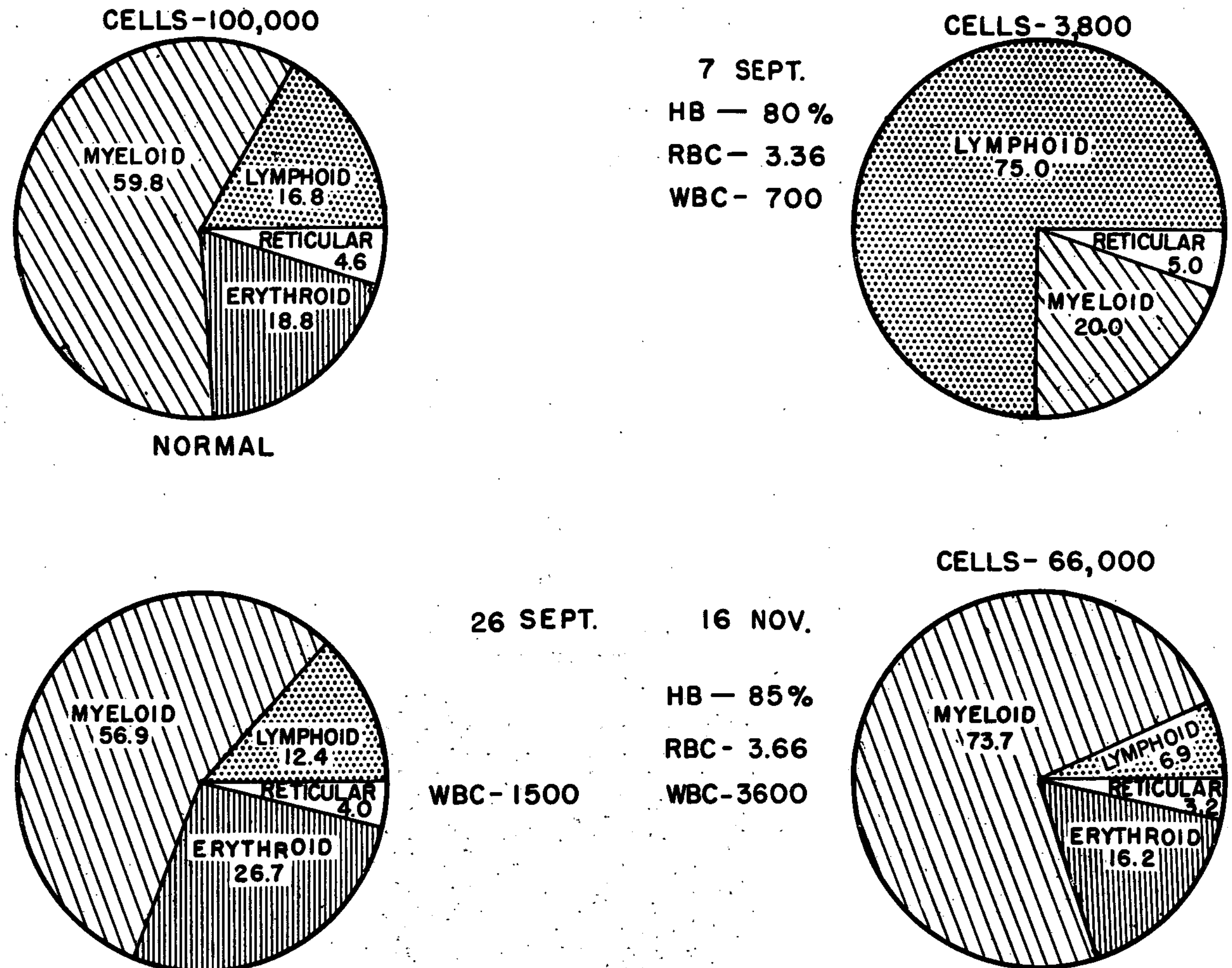


Fig. 5 (7)--(Photo File # NM 143.)

STERNAL MARROW BIOPSY



CASE: H-6030-U

Fig. 6 (7)

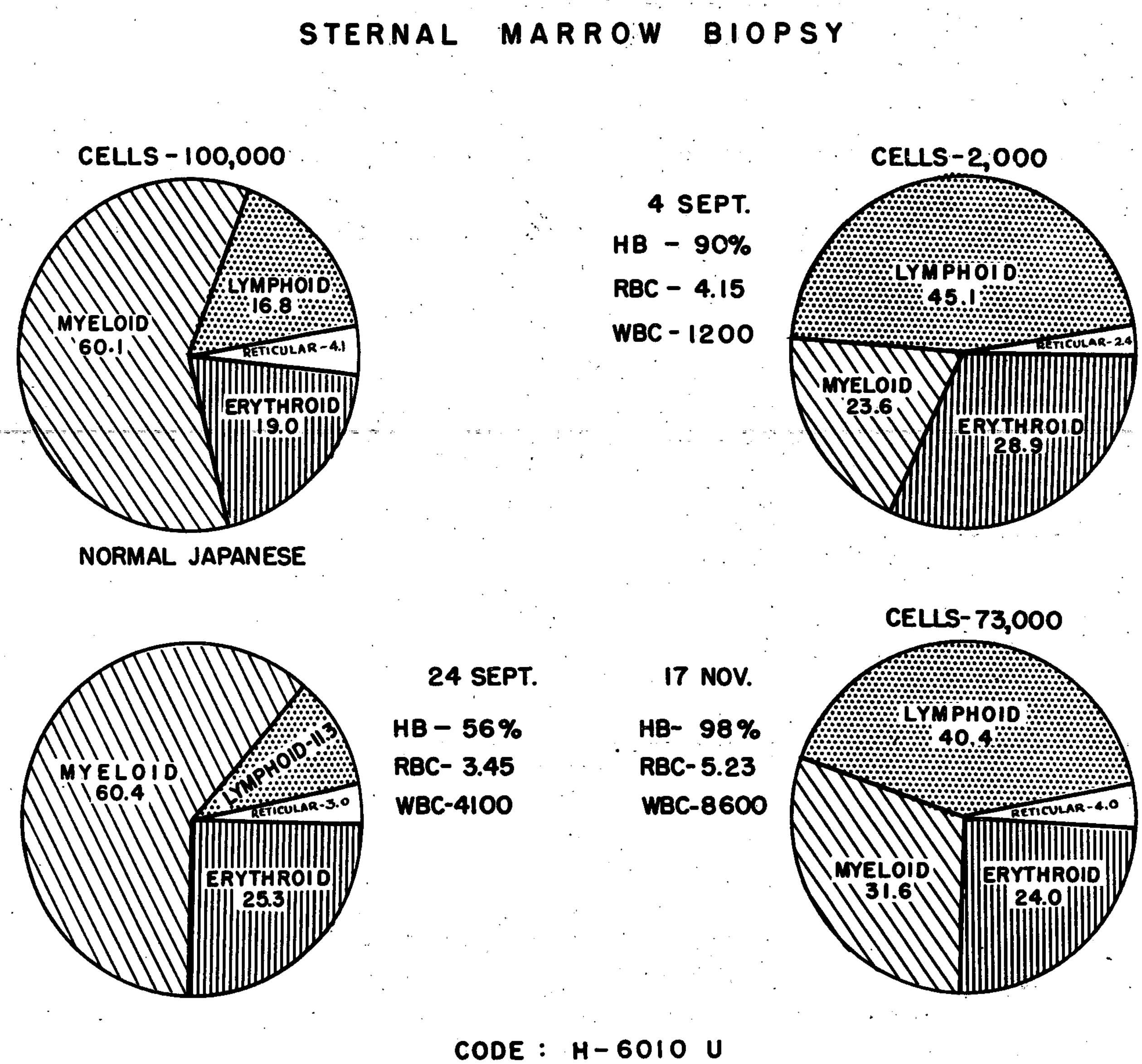


Fig. 7 (7)--(Photo File # HM 289.)

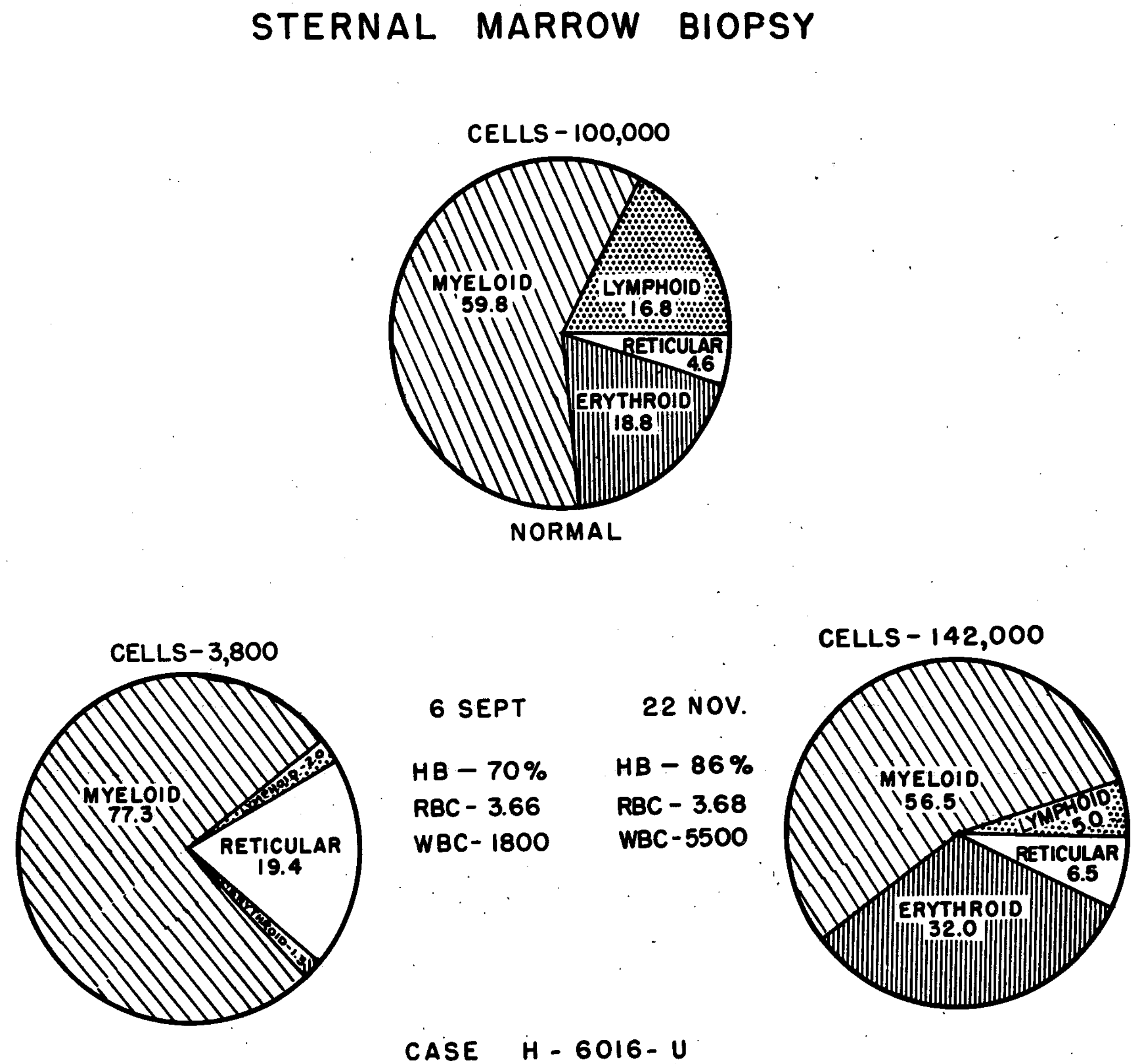
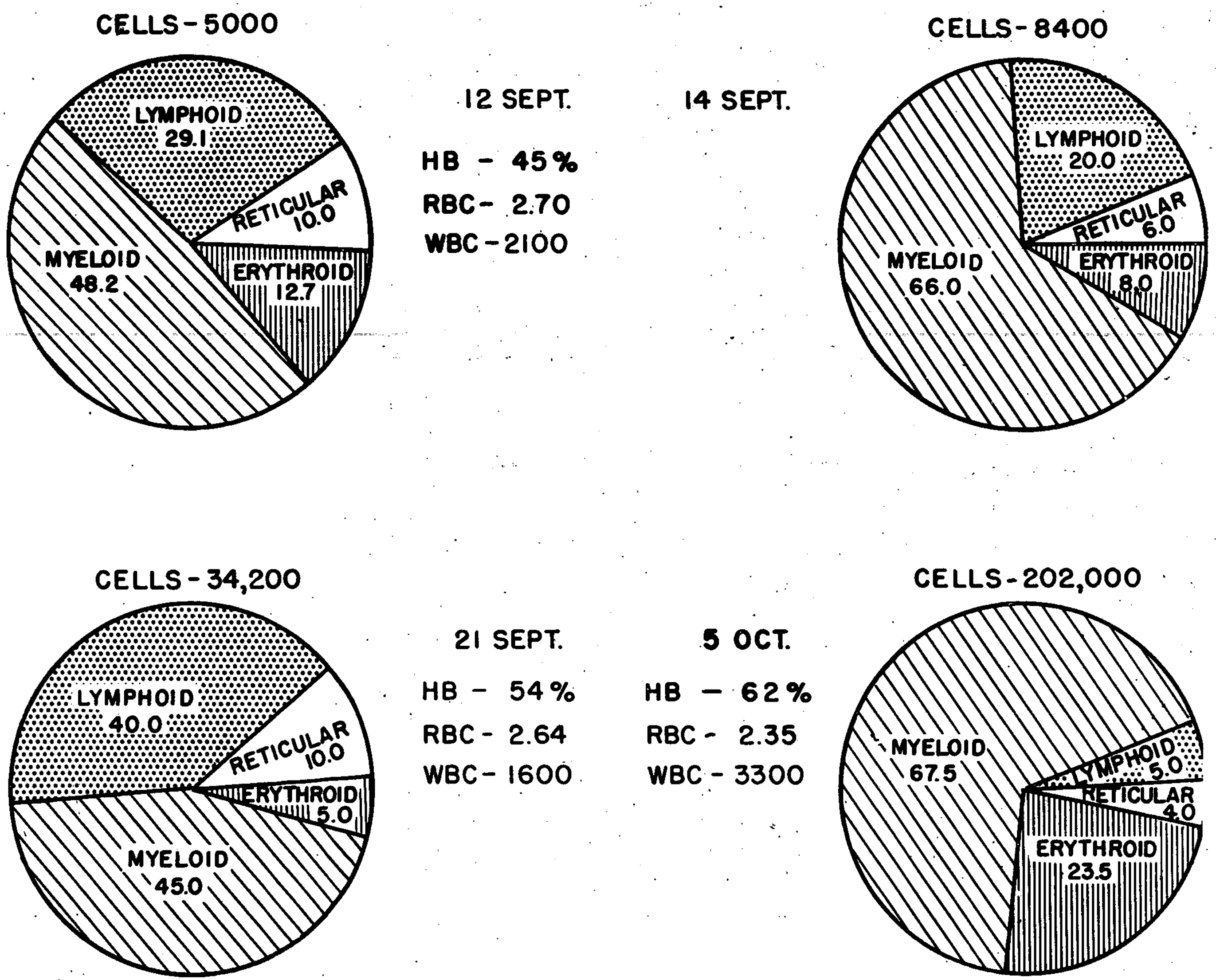


Fig. 8 (7)--(Photo File # HM 251.)

STERNAL MARROW BIOPSY



CASE K-49; CODE 02-10

Fig. 9 (7)--(Photo File # NM 144.)

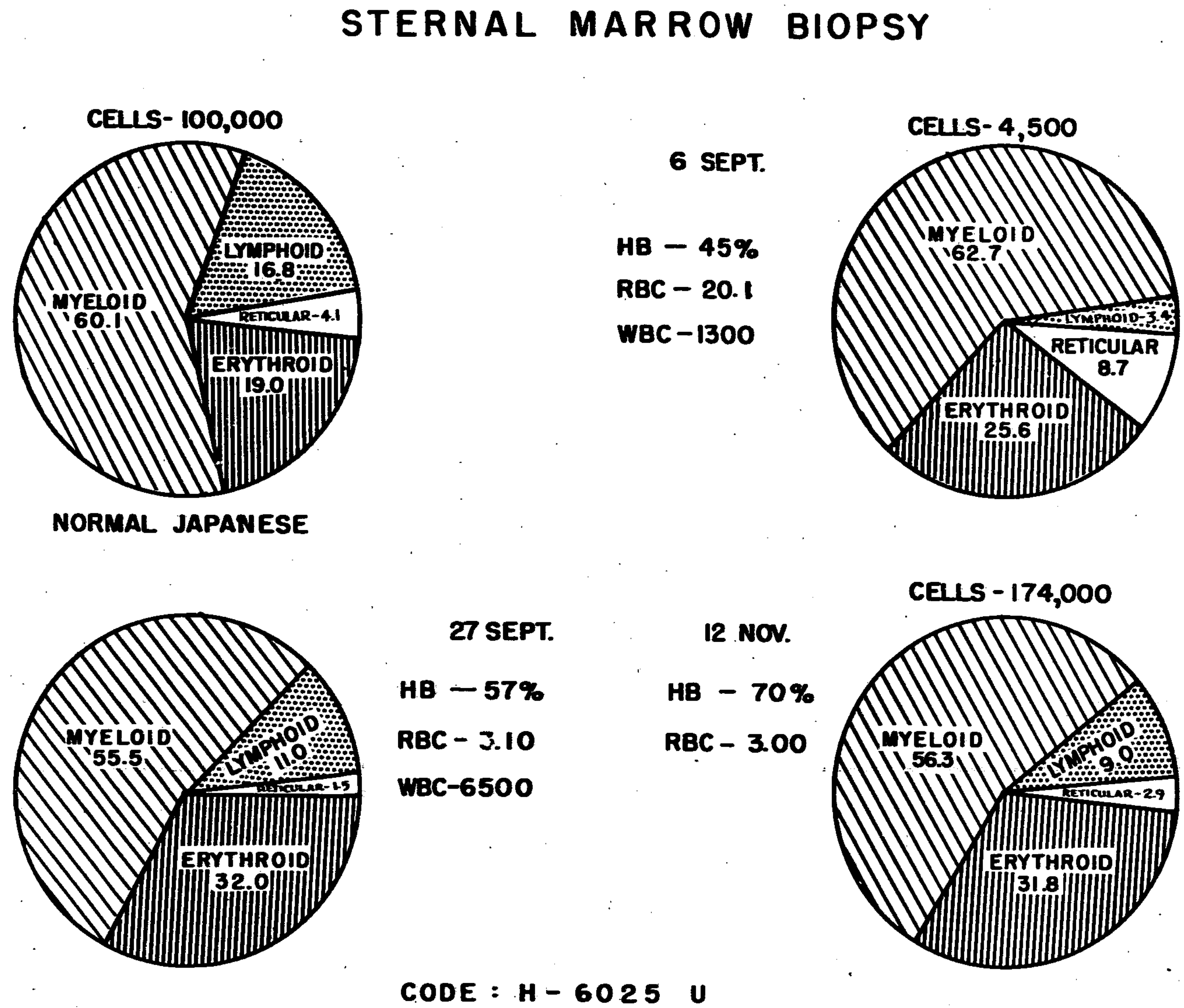


Fig. 10 (7)--(Photo File # HM 290.)

Fig. 11 (7)--Oura, K.I.U.-7, Distance ?. Marrow smear obtained post-mortem, 10 September, with 3 large reticulum cells, lymphocytes, and differentiating reticulum cells with azurophile granules. X 1000. (Photo File # NM 117K.)

Fig. 12 (7)--Oura, K.I.U.-7, Distance ?. Marrow smear obtained post-mortem, 10 September, showing 2 reticulum cells. The one on the left is the more mature. Differentiation into myelocytes is seen when nucleus has reached this stage of maturation. X 1000. (Photo File # NM 118K.)

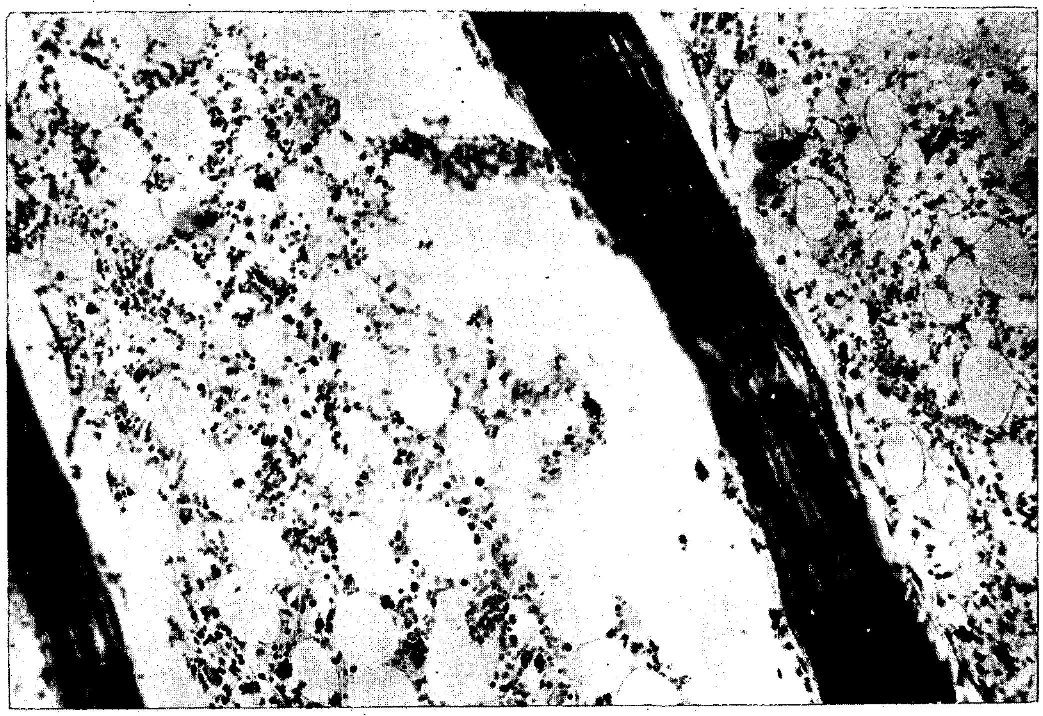


Fig. 13 (7)-- Takeuchi, 29. Male. 1000 meters. Died 4 September 1945. Rib marrow, showing hypoplasia and moderate congestion of the sinusoids. The mononuclear cells in the field are nearly all rectculum cells, plasma cells, or lymphocytes. X 180. Giemsa. Autopsy Key Number 39. (Photo File # HM 184K; AMM Acession 158930-103.)

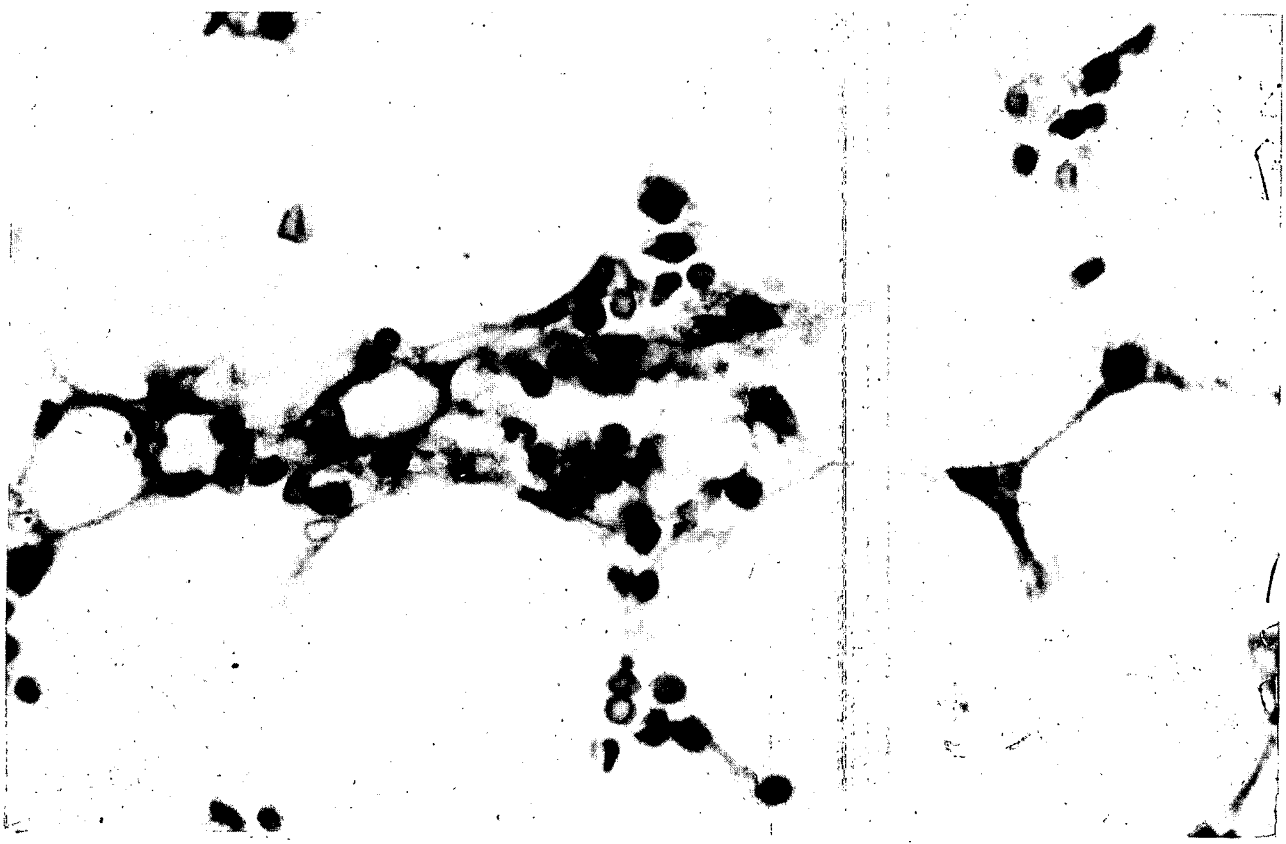


Fig. 14 (7)--Takeuchi, 29. Male. 1000 meters. Died 4 September 1945. Autopsy Key No. 39. Oil immersion field of section (Fig. 13) of rib showing the proliferation of reticulum and the collection of lymphocytes and plasma cells in "islands" between the fat cells. X 1200. Giemsa. (Photo File # HM 187K; AMM Accession 158930-103.)

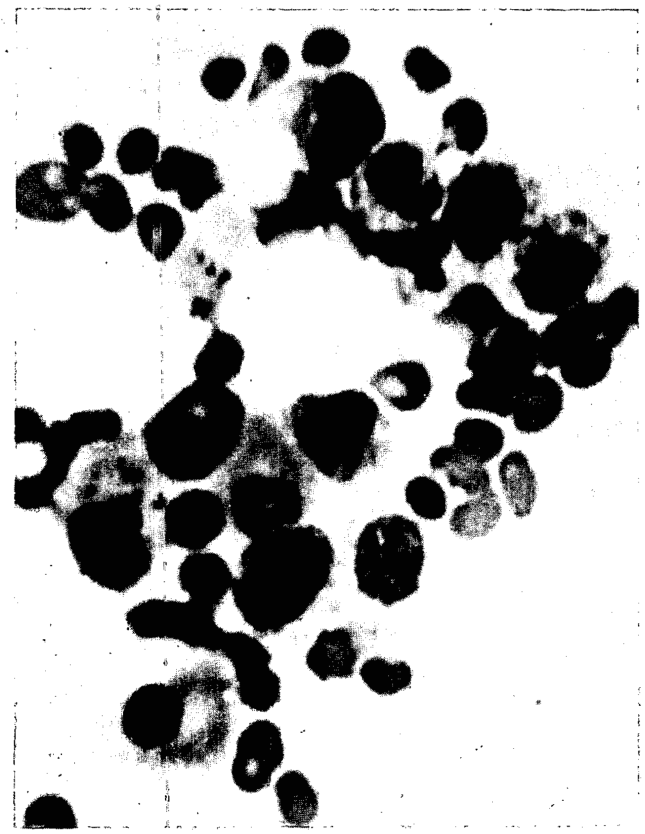


Fig. 15 (7)--Autopsy Key # 22. Omura, Age 22. Male. 1000 meters. Died 1 September 1945. Imprint smear of femoral marrow, showing macrophages (with and without pigment), plasma cells, and young myelocytes. X 1000. (Photo File # HM 249K; AMM Accession 158930-91.)

Fig. 16 (7)--Autopsy Key # 34. Fujita. Age 22. Male. Distance ?. Died 2 September 1945. Section of femoral marrow showing proliferating reticulo-endothelium and erythrophagocytosis. Notice the similarity in nuclear structure of the phagocytic cells and the reticulum cells. The relationship of the proliferation to the sinusoids is well shown. X 1000. (Photo File # HM 205K; AMM Accession 158930-98.)

Fig. 17 (7)--Oura, K.I.U.-7, Distance ?. Smear of sternal marrow obtained post-mortem, 10 September 1945, showing several types of plasma cells and reticulum cells. X 1200. (Photo File # NM 120K.)

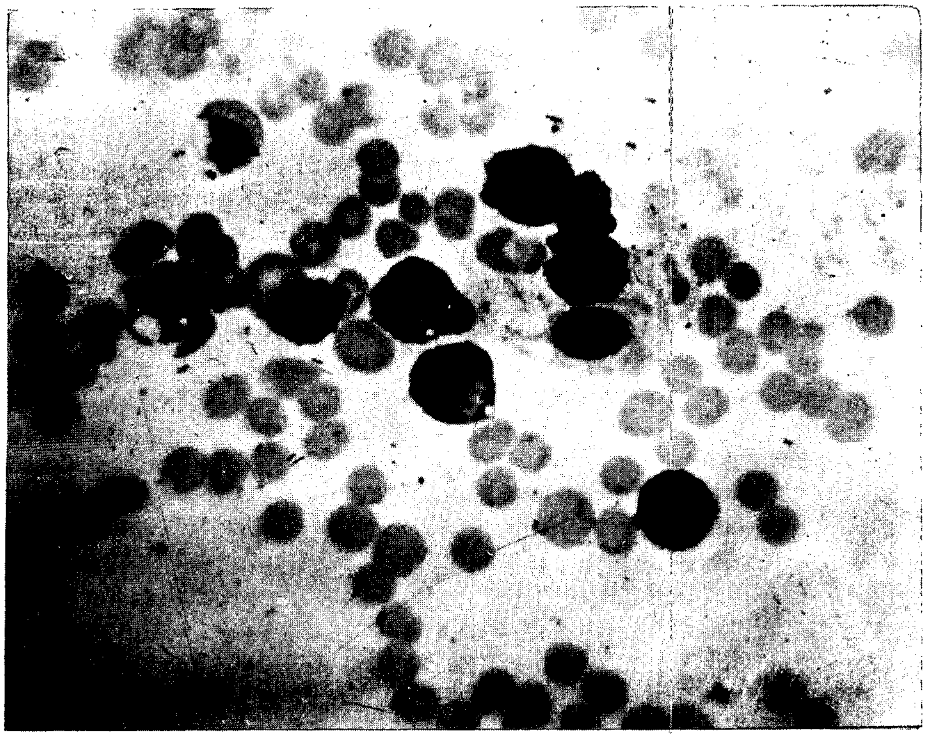


Fig. 18 (7)--Nichida. Age 33. Male. KUM-87. Distance 1200 meters. Smear of sternal marrow obtained 11 September. Total nucleated cell count: 173,000. Smear shows various types of plasma cells (5) and one reticulum cell. This patient recovered. See Table 11. X 1000. (Photo File # NM 129K.)

Fig. 19 (7)--Autopsy Key # 23. Satoi, ?. Male. 1000 meters. Died 31 August 1945. Section of femoral marrow showing the proliferation of reticulum and the development of plasma cells and lymphocytes in "islands" between the fat cells. Giemsa. X 1200. (Photo File # HM 192K; AMM Accession 158930-87.)

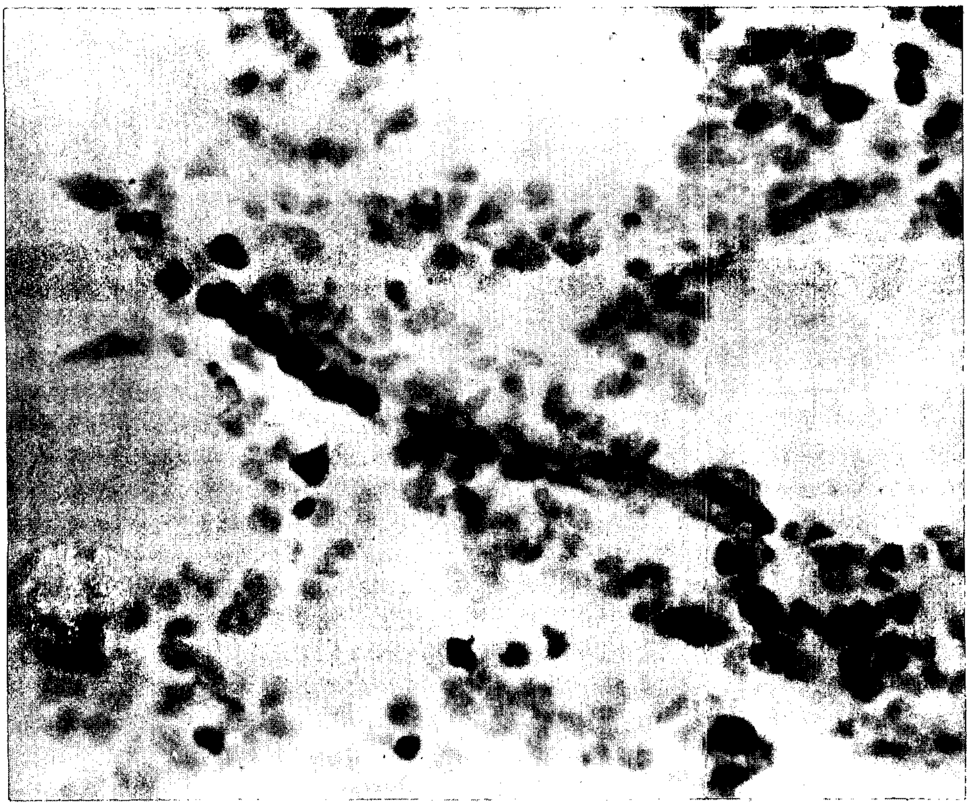


Fig. 20 (7)--Autopsy Key # 21. Iseoka. Age 45. Male. 1000 meters. Died 30 August 1945. Section of femoral marrow showing plasma cells arranged in a "string" along the endothelial wall of a capillary or a sinusoid. Giemsa. X 1200. (Photo File # HM 189K; AMM Accession 158930-85.)

Fig. 21 (7)--Autopsy Key # 21. Iseoka. Another field of section, Fig. 20, showing plasma cells in relation to reticulo-endothelium. Giemsa. X 1200. (Photo File # HM 190K; AMM Accession 158930-85.)

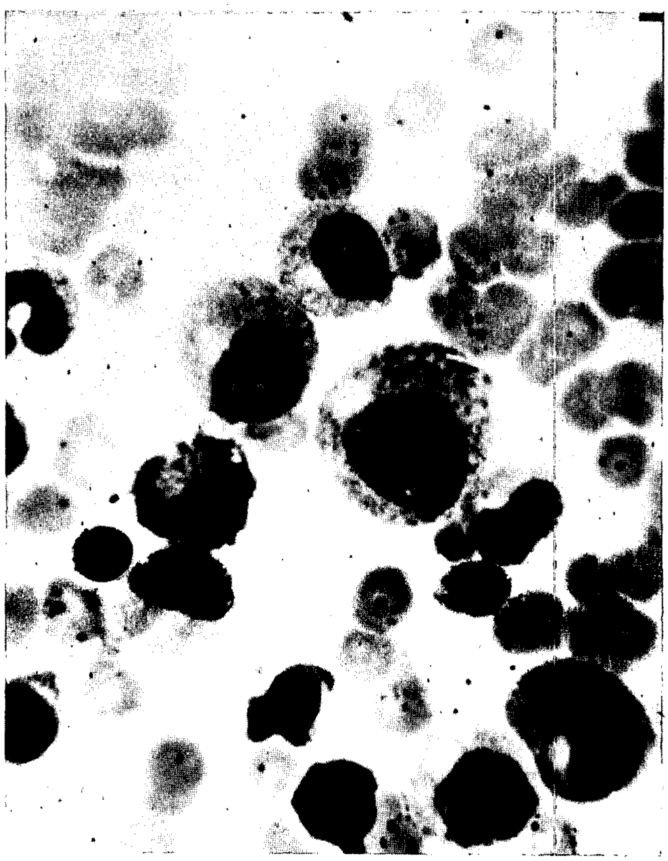


Fig. 22 (7)--Akamatsu. Age 21. Male. 1600 meters. Sternal biopsy, 7 September, showing the large abnormal lymphocytes. The cytoplasm of some of these is developing neutrophilic granulations. X 1500. (Case No. H-11879-KPS.) (Photo File # HM 160 K.)

Fig. 23 (7)--Yamashita. Age 17. Female. Distance ?. Sternal biopsy, 21 October, showing large abnormal lymphocytes without granules, also a reticulum cell. The character of the nucleus of the former type is the important feature. X 1500. (Case No. K.I.U.-33.) (Photo File # NM 113K.)

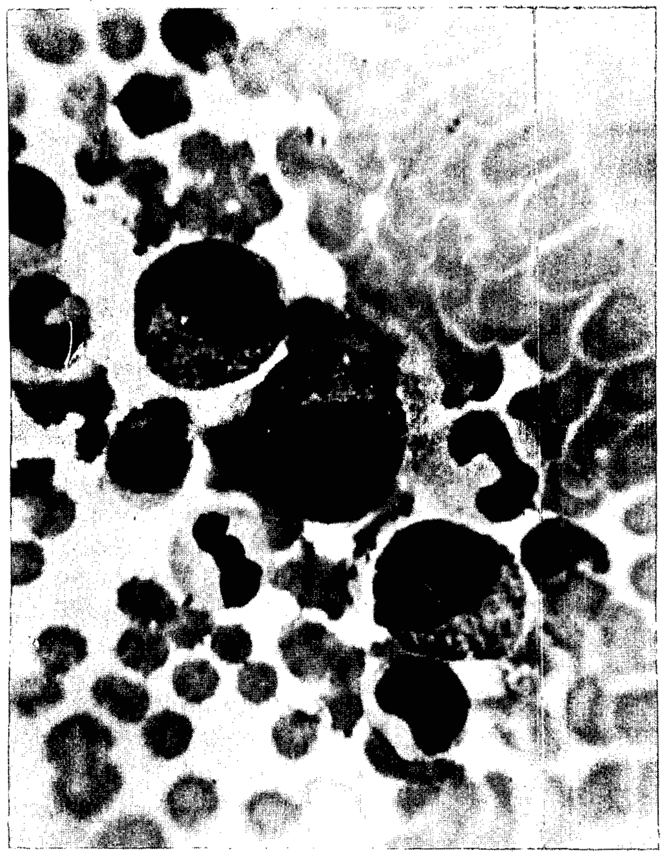


Fig. 24 (7)--Inoue. Age 46. Female. Less than 2000 meters. Sternal biopsy of 9 September, showing three large abnormal lymphocytes. The absence of granules and the flocculent nature of the cytoplasm and the comparatively coarse chromatin with inconspicuous nucleoli are the typical features. X 1500. (Case No. K.I.U.-19.) (Photo File #HM 177K.)

Fig. 25 (7)--Inoue. Age 46. Female. Another field from biopsy, Fig. 24, showing a large abnormal lymphocyte with a few azurophile granules. The coarse chromatin structure of the nucleus, and changing appearance of the cytoplasm are shown. X 1500. (Case No. K.I.U.-19.) (Photo File # HM 178K.)

Fig. 26 (7)--Hata. Age ?. Male. Less than 1200 meters. Sternal biopsy, 6 September, showing 3 large abnormal lymphocytes. The central one and the one on the right have a few azurophile granules in the cytoplasm. The reticular origin of these cells is suggested by the cell on the right. X 1500. (Case No. H-6016-U.) (See Case 6, Table 12B, and Fig. 8.) (Photo File # HM 156K.)

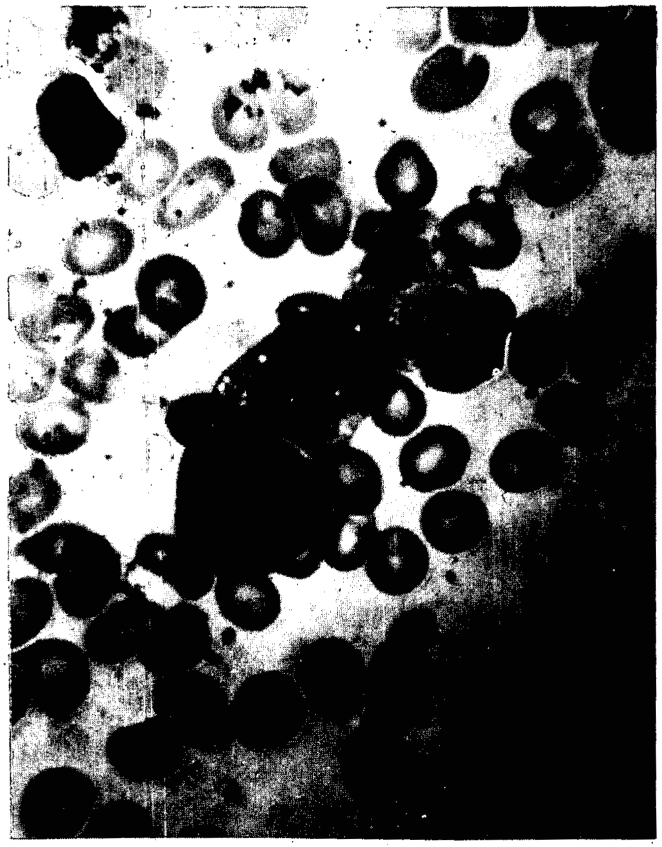


Fig. 27 (7)--Hata. Age ?. Male. Less than 1200 meters. Another field of the sternal biopsy smear, Fig. 26, showing more differentiated stages of the abnormal lymphocyte, which here resembles a metamyelocyte. The nuclear structure, however, resembles that seen in Fig. 26. X 1500. (Case H-6016-U.) (Photo File # HM 155K.)

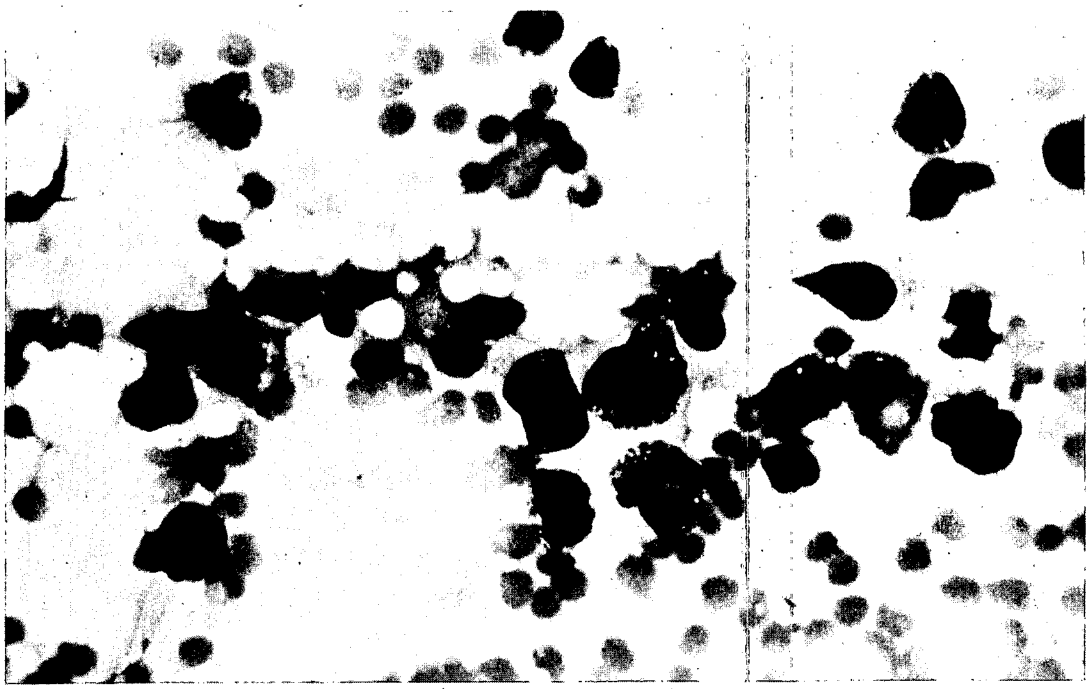


Fig. 28 (7)--Autopsy Key # 28. Kawaura. Age 23. Male. 1000 meters. Died 1 September 1945. Smear of vertebral marrow showing reticulum cells, abnormal lymphocytes, and the apparent relation of these to each other. There are also plasma cells and small lymphocytes. X 1000. (Photo File # HM 201K; AMM Accession 158930-92.)

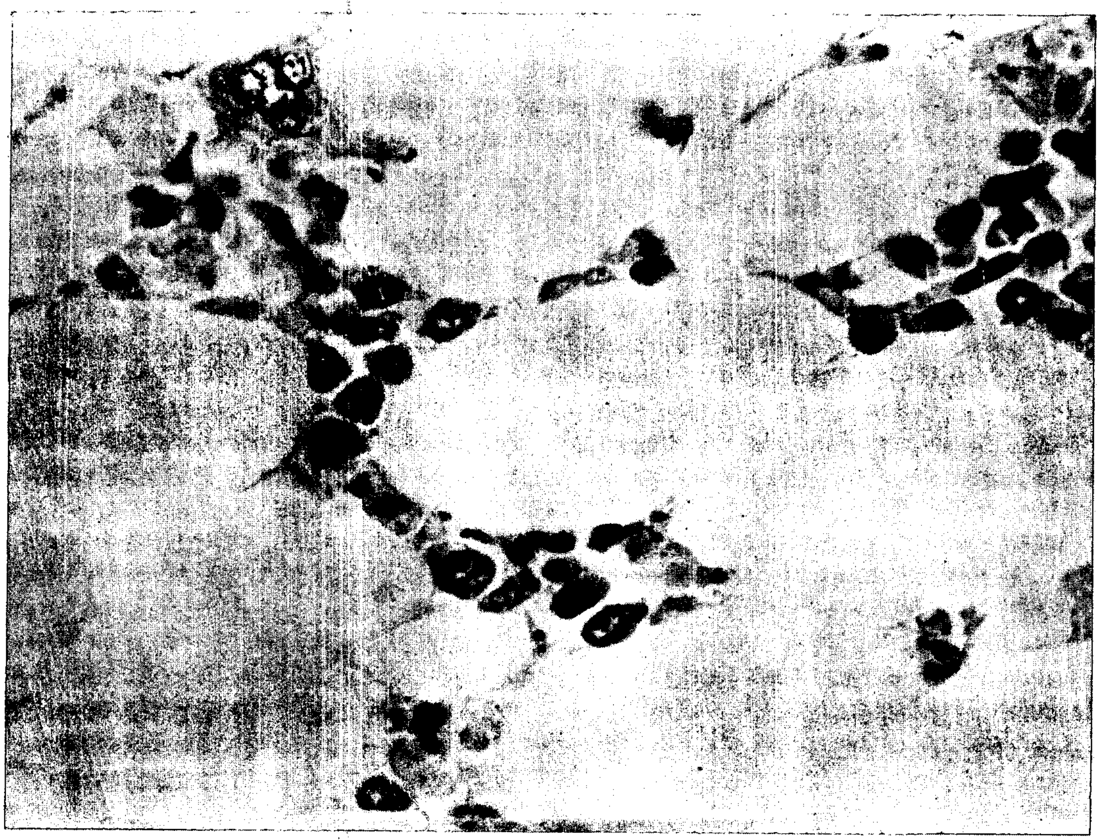


Fig. 29 (7)--Satoi. Age ?. Male. 1000 meters. (See Fig. 19.) Another portion of section, Fig. 16, showing large (abnormal) lymphocytes occurring in association with proliferating reticulum in "islands" between the fat cells. Giemsa. X 1200. (Photo File # HM 193K; AMM Accession 158930-87.)

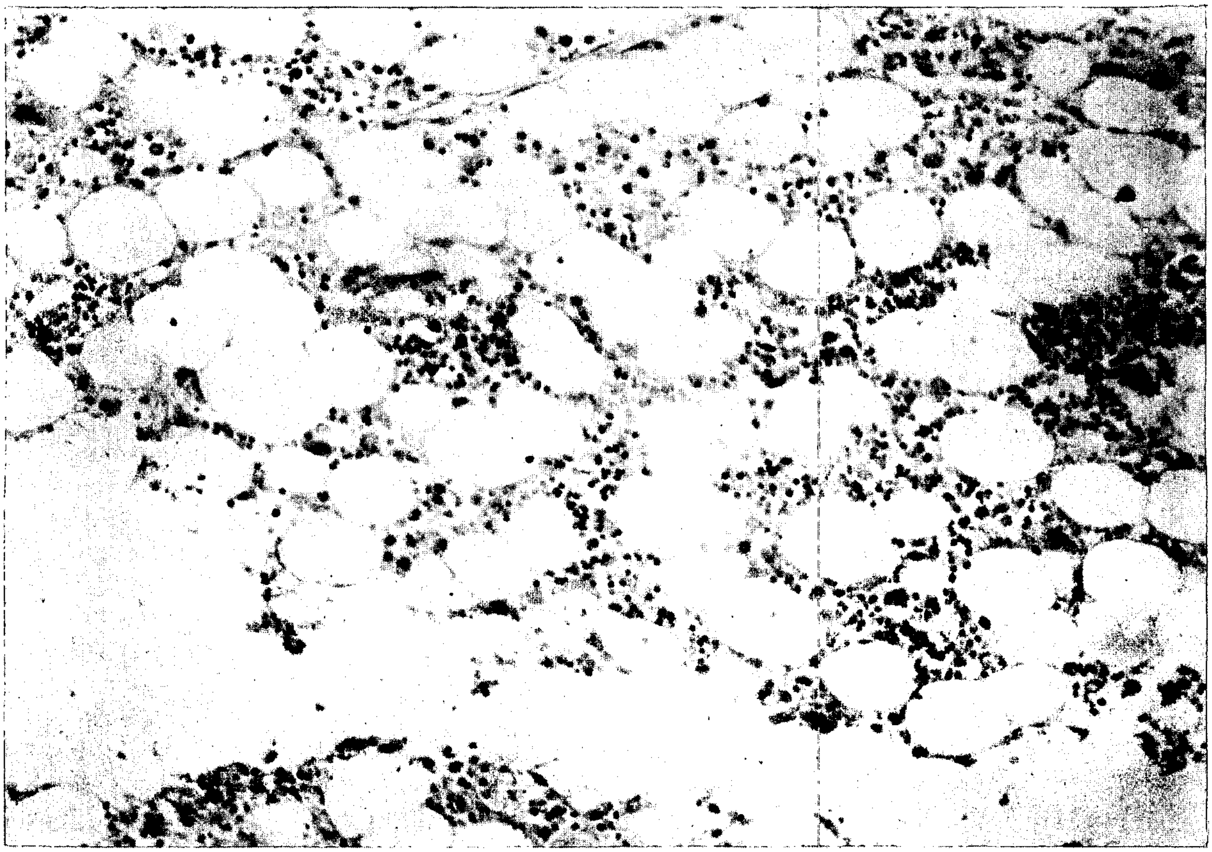


Fig. 30 (7)--Fujita, Age 22. Sex ?. Distance ?. Died 2 September 1945. Section of femoral marrow showing small scattered groups of erythropoiesis as well as proliferated reticulum and occasional lymphocytes and plasma cells. X 230. (Photo File # HM 207K.)

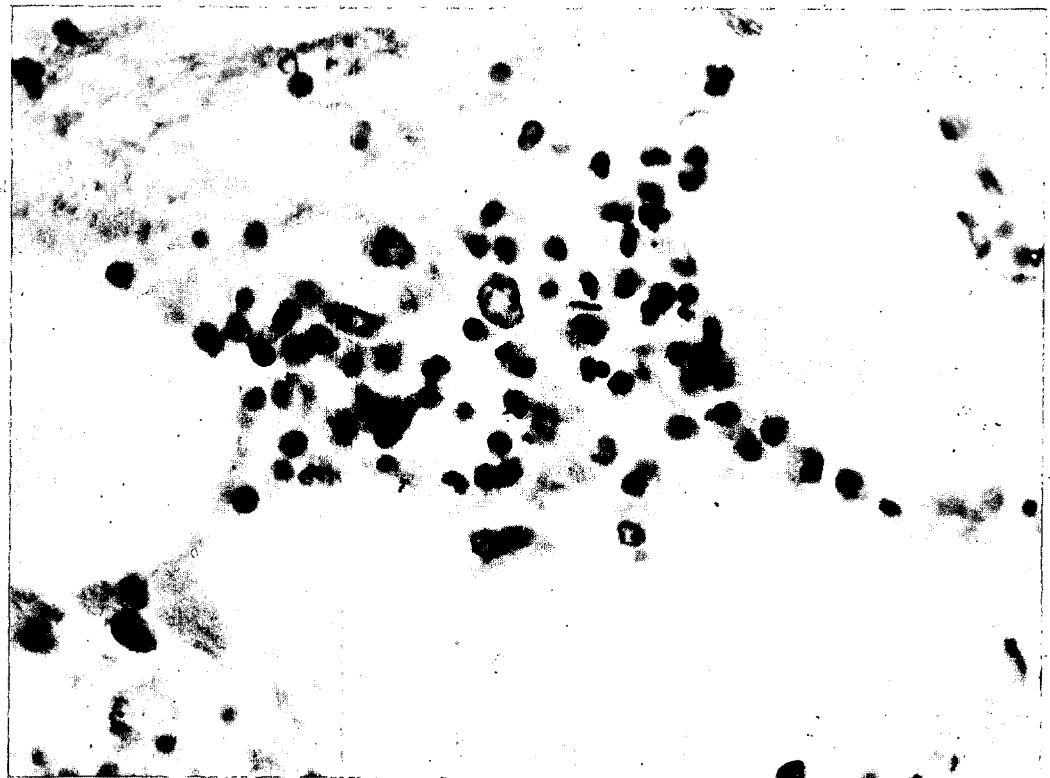


Fig. 31 (7)--Fujita. Age 22. Sex ?. Distance ?. (see Fig. 30). Oil immersion view of a portion of section (Fig. 30) showing the proliferating reticulum, lymphocytes, and small irregularly arranged group of nucleated red cells, most of which appear to be polychrome normoblasts. X 1000. (Photo File # HM 206K.)

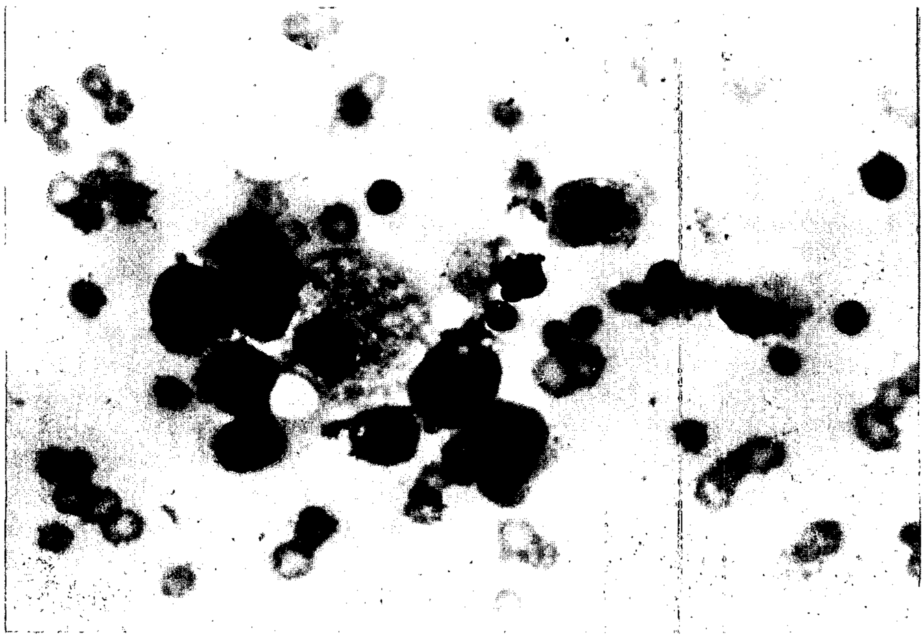


Fig. 32 (7)--Horinouchi. Age 33. Male. 1000 meters. Died 7 September 1945. Smear of sternal marrow showing several types of reticulum cells. The 3 cells on the left have the same type of nucleus, but more condensed cytoplasm containing azurophile granules. These are thought to be early myelocytes developing directly from reticulum. X 1000. (Photo File # HM 321K.)

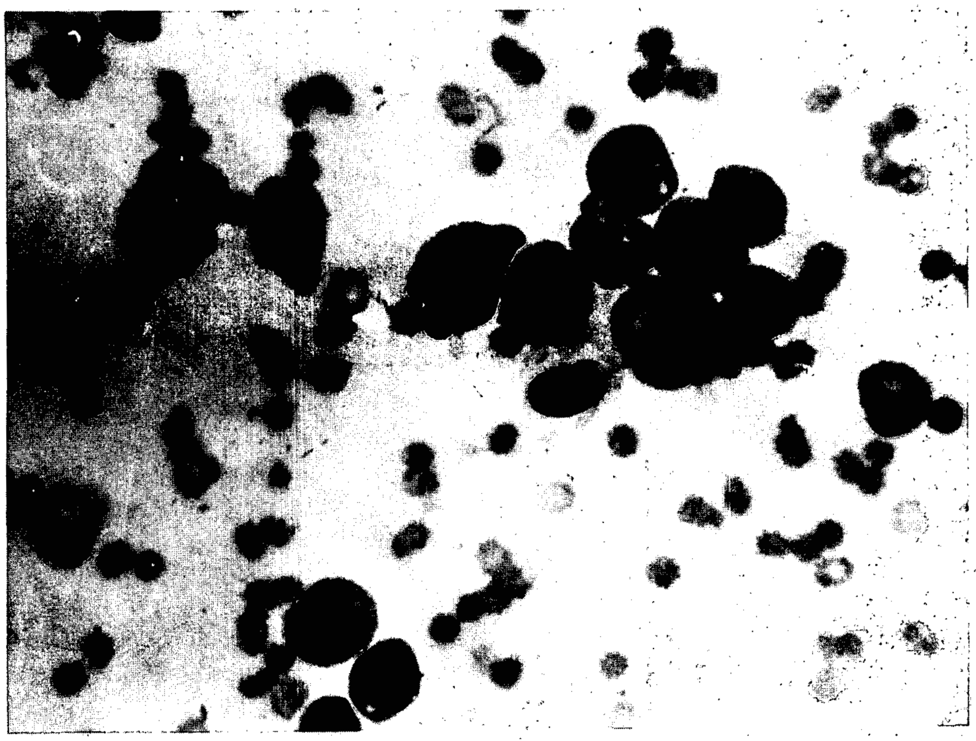


Fig. 33 (7)--(see Fig. 32). Horinouchi. Age 33. Male. 1000 meters. Another field from smear shown in Fig. 32. The reticulum cells in this smear are quite distinct, and these are many with azurophile granules in the cytoplasm, early myelocytes. X 1000. (Photo File # HM 319K.)

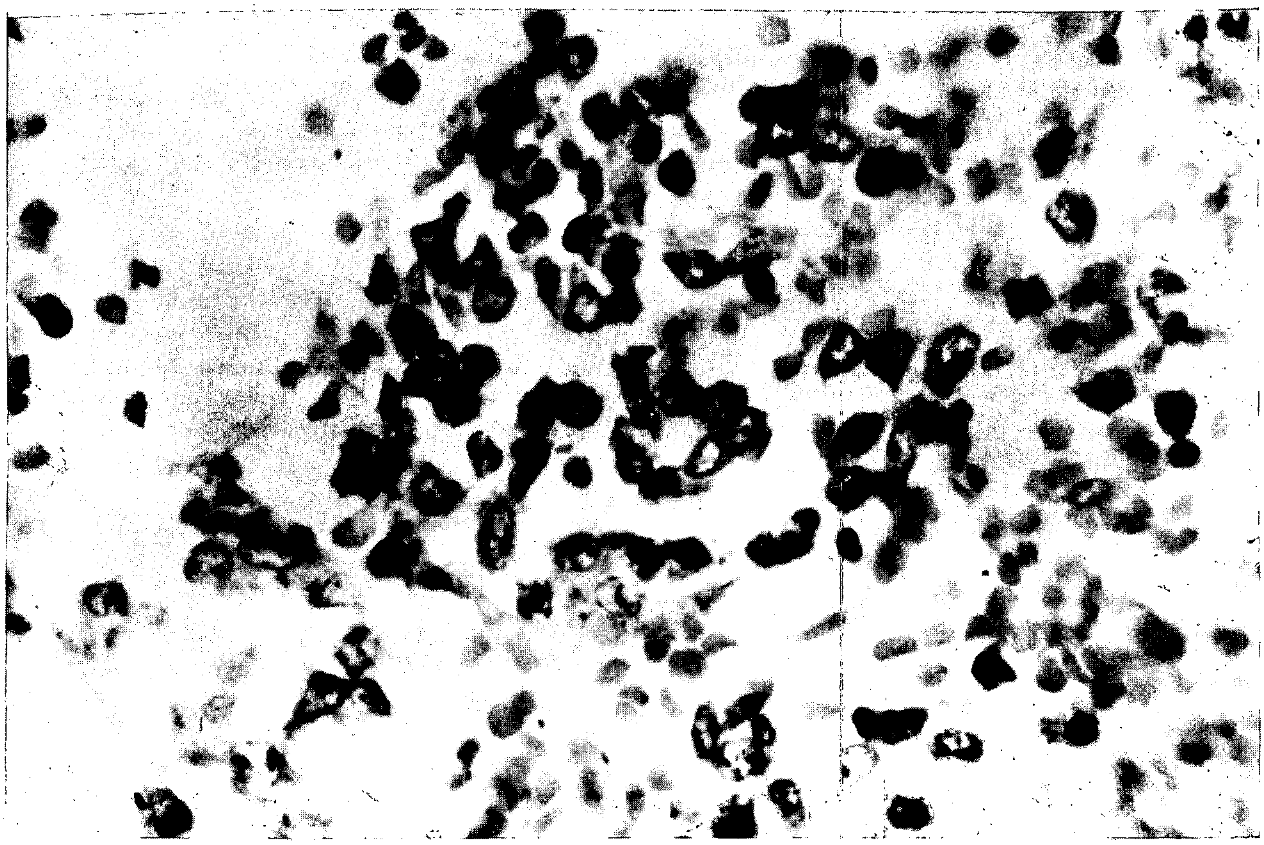


Fig. 34 (7)--Autopsy Key # 22. Michihara. Age ?. Male. 1000 meters. Died 3 August 1945. Section of vertebral marrow showing relatively cellular tissue. The nuclear structure of the cells varies from typically reticular to early myelocytic in type. Giemsa. X 1200. (Case No. H-6160-U.) (Photo File # HM 181K; AMM Accession 158930-86.)

Fig. 35 (7)--Autopsy Key # 22. Michihara. Age ?. Male. 1000 meters. Died 3 August 1945 (see Fig. 34). Imprint smear of vertebral marrow shown in section in Fig. 34. The photomicrograph shows a series of intergradations between reticulum cells and more differentiated types with azurophile granules that resemble myelocytes. X 1500. (Photo File # HM 170K; AMM Accession 158930-86.)

Fig. 36 (7)--Autopsy Key 22. Michihara. Age ?. Male. 1000 meters. Died 3 August 1945 (see Fig. 34). Imprint smear of vertebral marrow shown in section in Fig. 34. More examples of the metamorphosis of reticulum cells into myelocytes. X 1500. (Photo File # HM 171K; AMM Accession 158930-86.)

Fig. 37 (7)--Autopsy Key # 22. Michihara. Age ?. Male. 1000 meters. (see Fig. 34.) Imprint smear of vertebral marrow shown in section in Fig. 34. In this field plasma cells and reticulum cells and one myelocyte are shown for contrast. X 1500. (Photo File # HM 172K; AMM Accession 158930-86.)

Fig. 38 (7)--Oura, K.I.U.-7, Distance ?. Sternal marrow smear showing a group of cells with typically reticular nuclei and varying amounts of azurophile granulation, and one with none. Plasma cells and small lymphocytes are also shown. X 1500. (Photo File # NM 119K.)

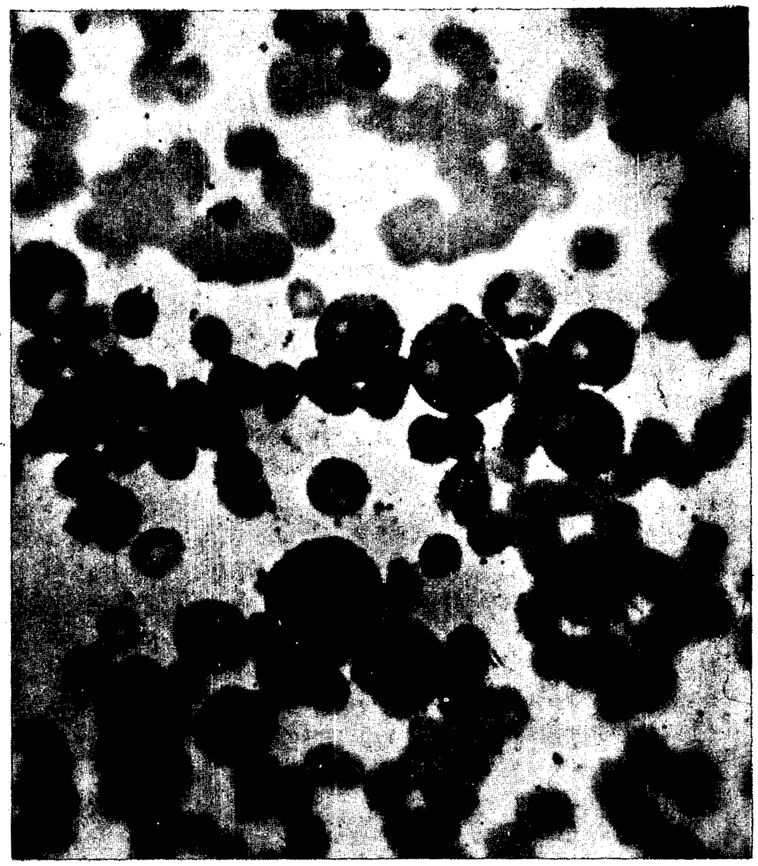


Fig. 39 (7)--Nichida. Age 33. Male. Less than 1200 meters. Sternal biopsy of 19 September (see Fig. 18 for early biopsy) when total nucleated cell count was 68,000. The smear shows one large abnormal lymphocyte and several metamyelocytes of the sort that develop from the former cell. Notice the quality of the cytoplasm in the metamyelocytes and the persistence of azurophile granules. X 1200. (See also Case (1), Fig. 4c, Table 2.) (Case No. KUM-87.) (Photo File # NM 131K.)

Fig. 40 (7)--Dobi. Age 20. Female. 1100 meters. Sternal biopsy, 18 October 1945, showing abnormal lymphocytes, the myelocytes and metamyelocytes with conspicuous azurophile granules. One myelocyte of the type that develops from the abnormal lymphocyte is shown with two nuclei. The basophilic erythroblast is normal. X 1500. (Case No. 3058.) (Photo File # NM 134K.)

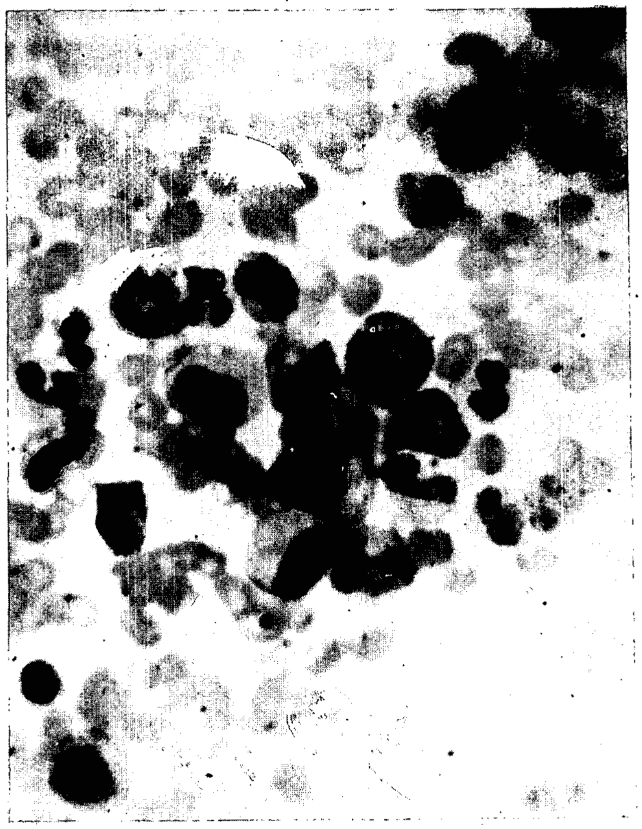


Fig. 41 (7)--Fukabori. Age 33. Female. 1300 meters. Sternal biopsy, 16 December 1945, showing the persistence of the abnormal lymphocytes and plasma cells. (Photo File # NM 122K.)

Fig. 42 (7)--Yamaguti. Age 35. Male. Distance ?. Sternal biopsy, 5 October, at which time the total nuclear cell count was 202,000. The smear shows a normal 'blast and quite normal stages of granulocyte development. This patient had a reticular marrow 4 weeks before. (Case No. K.I.U.-49. See also Fig. 9 and Table 13.) (Photo File # NM 128K.)

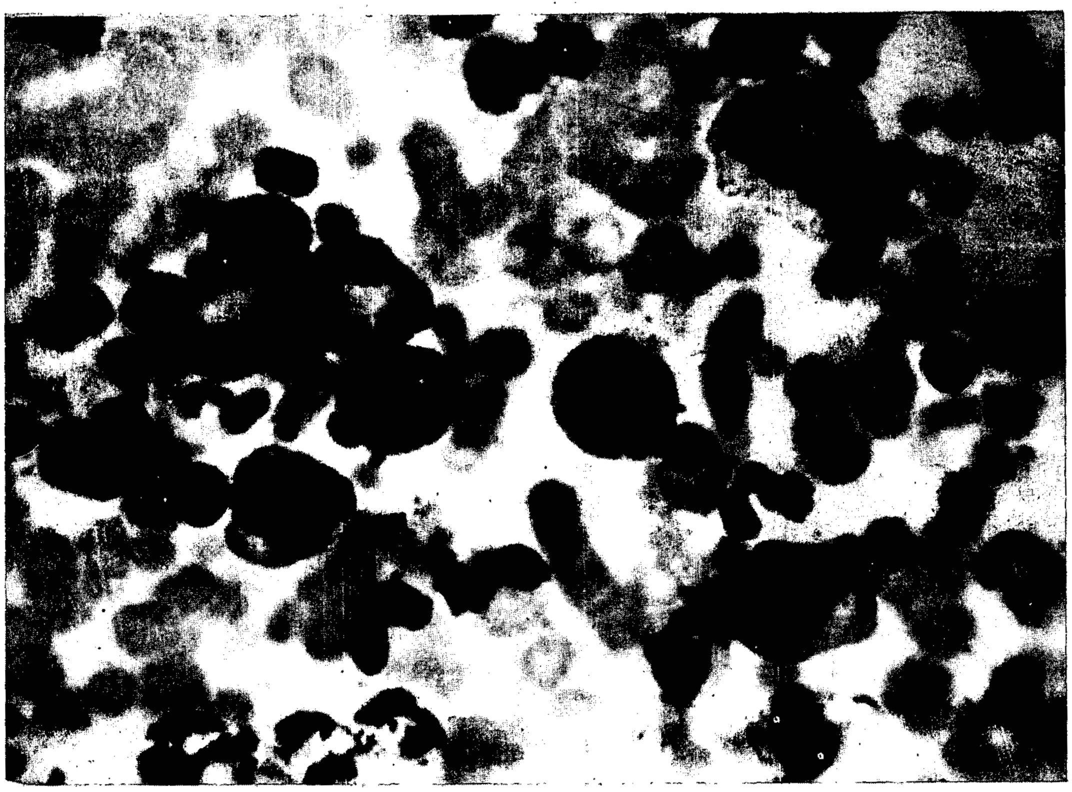


Fig. 43 (7)--Nakazima. Age 16. Male. 1300 meters. Sternal biopsy, 16 October, showing active regeneration with normal appearing 'blasts and granulocytes. The red cell series also appears normal. X 1500. (Case No. 278.) (Photo File # NM 136K.)

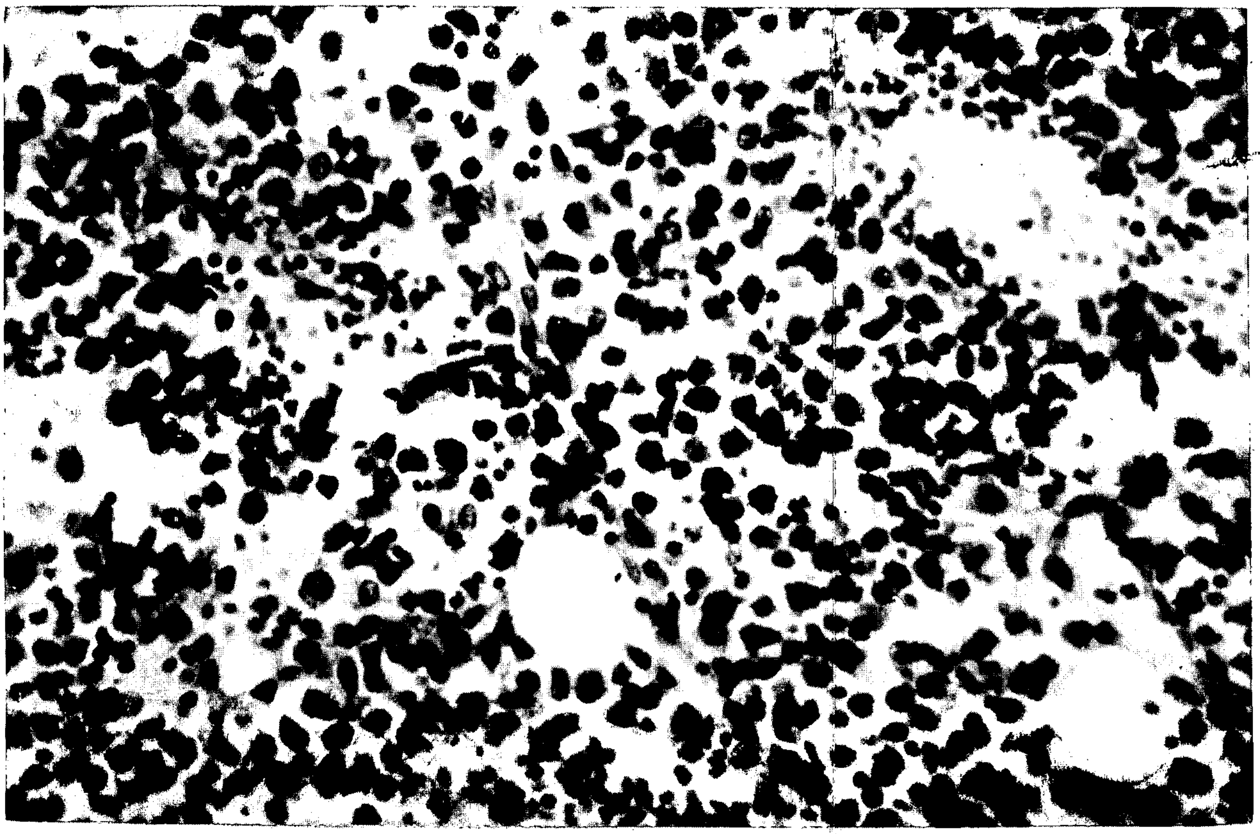


Fig. 44 (7)--Fukabori, Age 8. Female. 700 meters. Died 4 October 1945. Sternal marrow showing proliferating reticulum and many eosinophilic granulocytes of all stages. X 550. (Photo File # HM 150K; AMM Accession 158930-194.)

Fig. 45 (7)--Akamatsu. Age 21. Male. 1600 meters. Sternal biopsy, 12 September (see Fig. 22) showing very early forms of erythroblasts, whose nuclei bear a close resemblance to those of reticulum cells. X 1500. (Case No. H-11879-KPS.) (Photo File # HM 159K.)

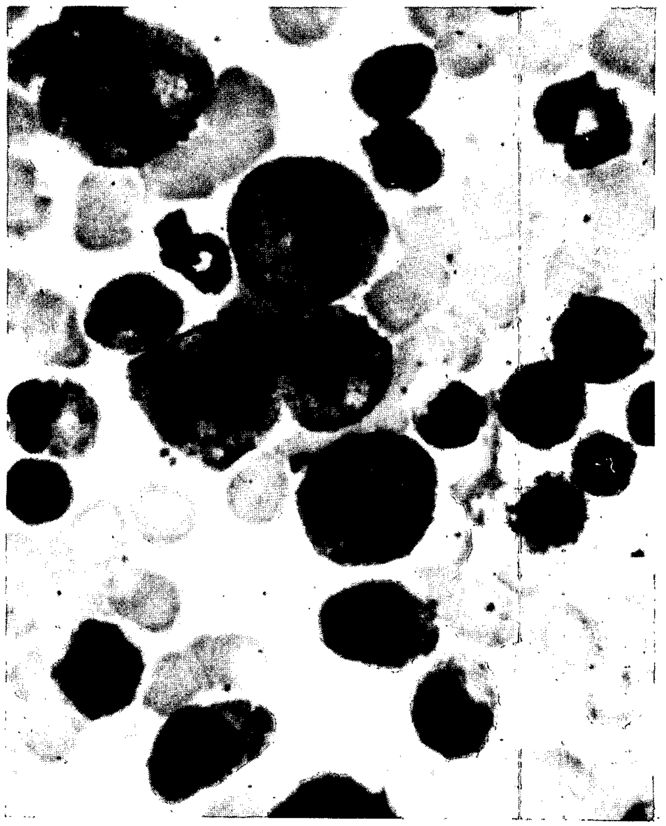


Fig. 46 (7)--Hata. Age ?. Male. Less than 1200 meters. Sternal biopsy, 6 September (see Figs. 26, 27), showing young erythroblasts whose nuclei retain the appearance of reticulum. Notice the cell with azurophile granules, but with other features resembling the erythroblasts. [Case No. H-6016-U (Case 5, Table 12b, and Fig. 8).] (Photo File # HM 158K.)

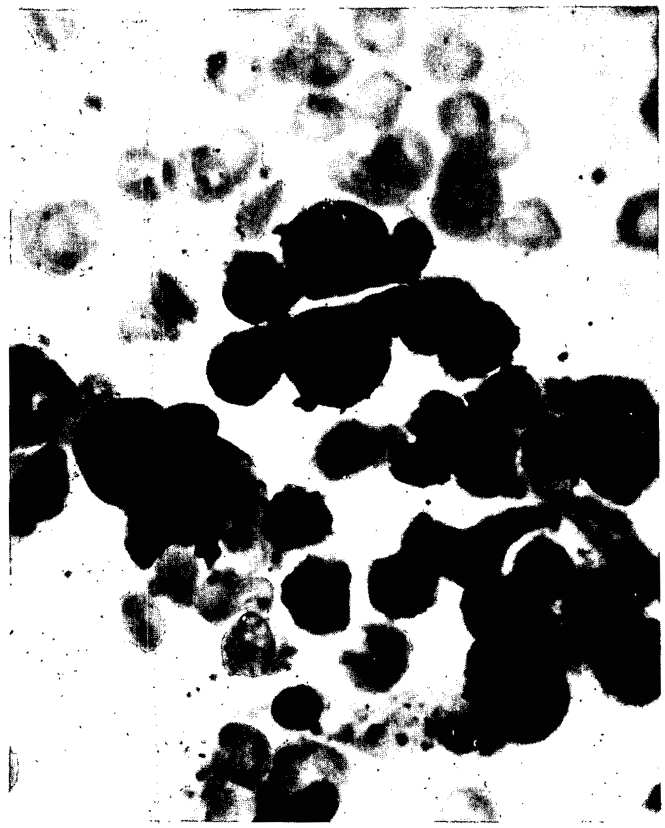


Fig. 47 (7)--Ishii. Age 23. Male. 1000 meters. Sternal biopsy, 24 September 1945, showing a group of erythropoietic cells. The basophilic erythroblasts (or pronormoblasts) have a normal appearance as do the more mature stages. X 1500. (Case No. H-10335-U.) (See also Table 22c.) (Photo File # HM 162K.)

Fig. 48 (7)--Ishii (see Fig. 27). Age 23. Male. 1000 meters. Another field, sternal biopsy, 24 September 1945. Mitosis in normal appearing basophilic erythroblasts. X 1500. (Case No. H-10335-U.) (Photo File # HM 163K.)

Fig. 49 (7)--Ishii. Age 23. Male. 1000 meters. Another field, sternal biopsy, 24 September 1945, showing more matured forms of nucleated red cells than those in Figs. 47 and 48. Some of the polychrome normoblasts are unusually large, but the nucleus is of the ordinary heteroplastic type. X 1500. (Photo File # HM 161K.)

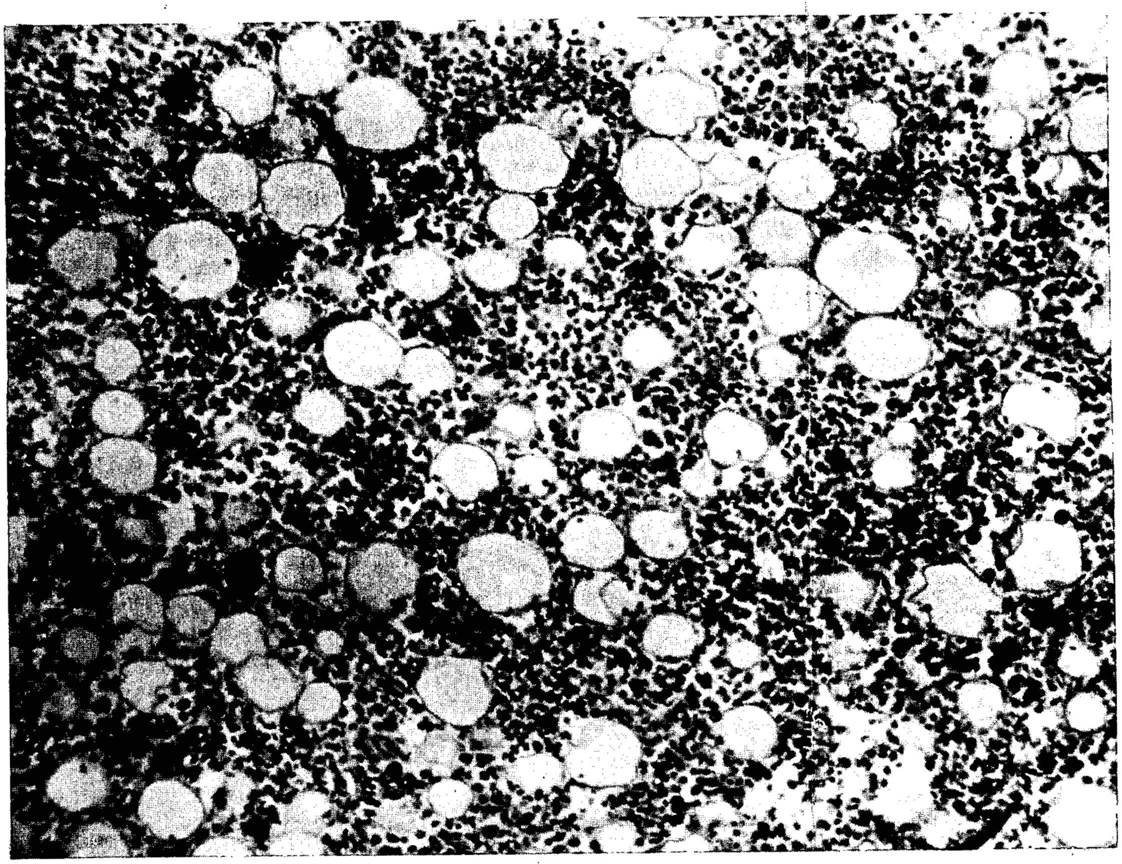


Fig. 50 (7)--Kinoshita. Age 58. Male. 1300 meters. Died 18 November 1945. Rib marrow showing scanty cellularity generally. There are very few polys, and the majority of cells are large mononuclears. Notice the diffuse distribution of the erythropoietic elements. X 190. (Omura Naval Hospital Case No. 10.) (Photo File # NM 157K; AMM Accession 158930-190.)

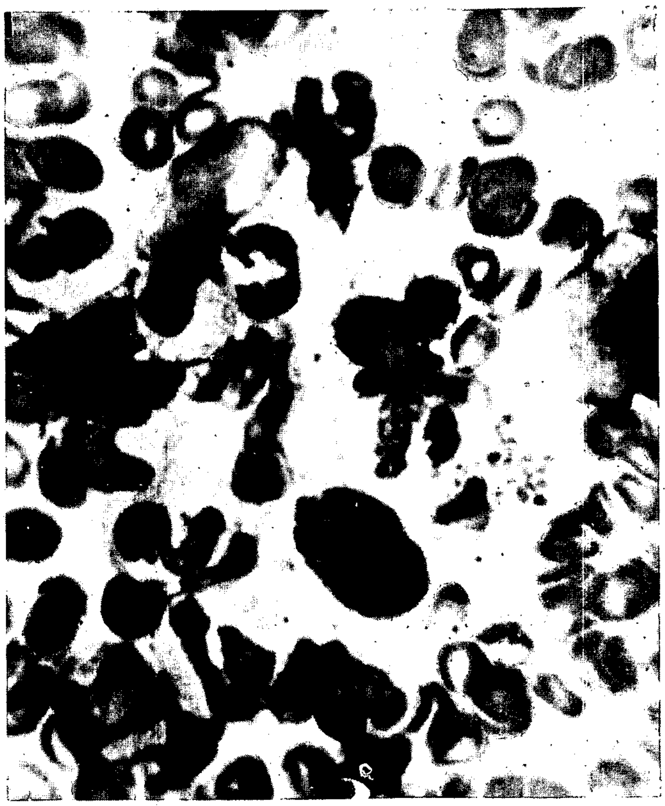


Fig. 51 (7)--Kazuko. Age 19. Female. 200 meters. Sternal biopsy, 19 November, showing the unusual number of abnormal lymphocytes. The granulocytic cells appear normal. X 1500. (Case H-10616-I.) (Photo File # HM 169K.)

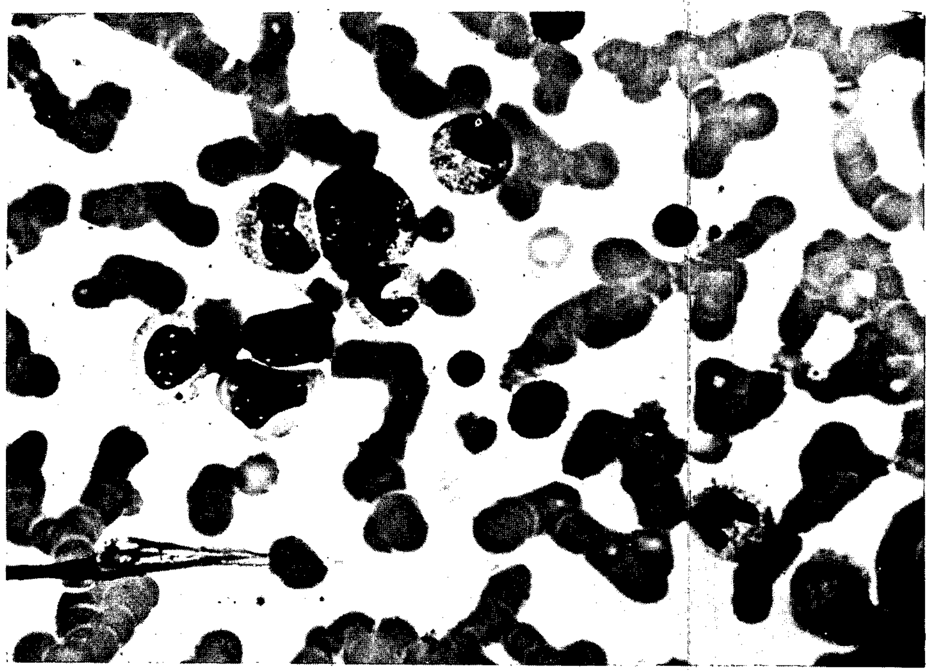


Fig. 52 (7)--Kijima, 31. Male. 1000 meters. Died 15 November 1945. Autopsy Key # 50. Imprint smear of sternal marrow showing 3 cells resembling atypical (abnormal) lymphocytes, a myelocyte, 2 stab forms, and a metamyelocyte. X 1500. (Photo File # HM 309K; AMM Accession 158930-66.)

Fig. 53 (7)--Kijima. Age 31. Male. Autopsy Key # 50. 1000 meters. Another field (see Fig. 52) showing 2 cells with nucleus and cytoplasm closely resembling that of the abnormal lymphocytes in Fig. 52, but with definite neutrophil granulation around and over the nucleus. The other 3 myelocytes have more general granulation. X 1500. (Photo File # HM 312K; AMM Accession 158930-66.)

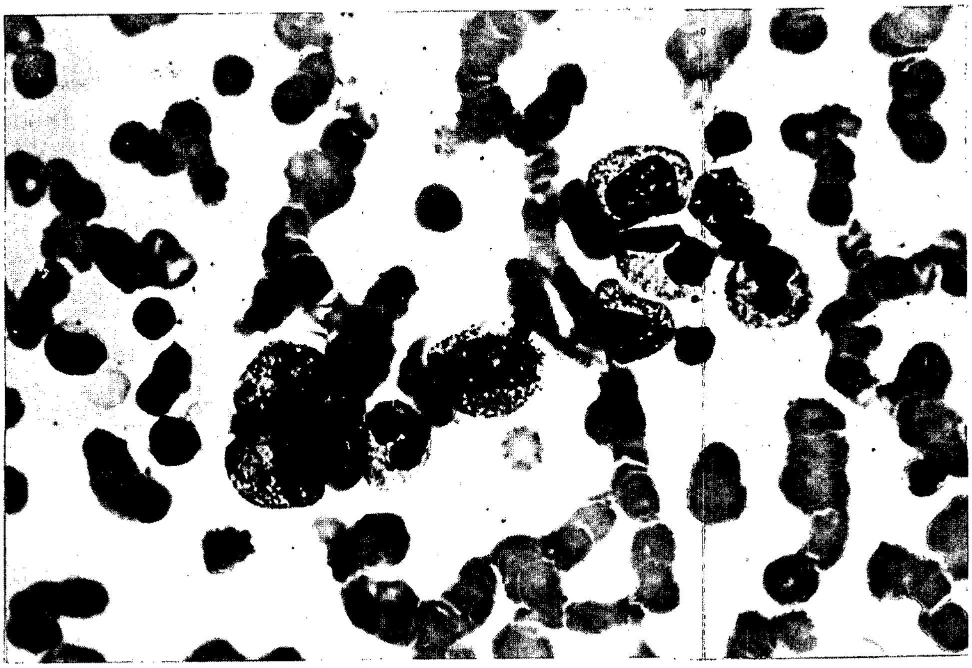


Fig. 54 (7)--Autopsy Key # 50. Kijima. Age 31. Male. 1000 meters. Another field, same smear as Fig. 52, showing more of the lymphocyte-like forms with neutrophil granules. All the cells except the central one are readily recognized as myelocytes. X 1500. (Photo File # HM 311K; AMM Accession 158930-66.)

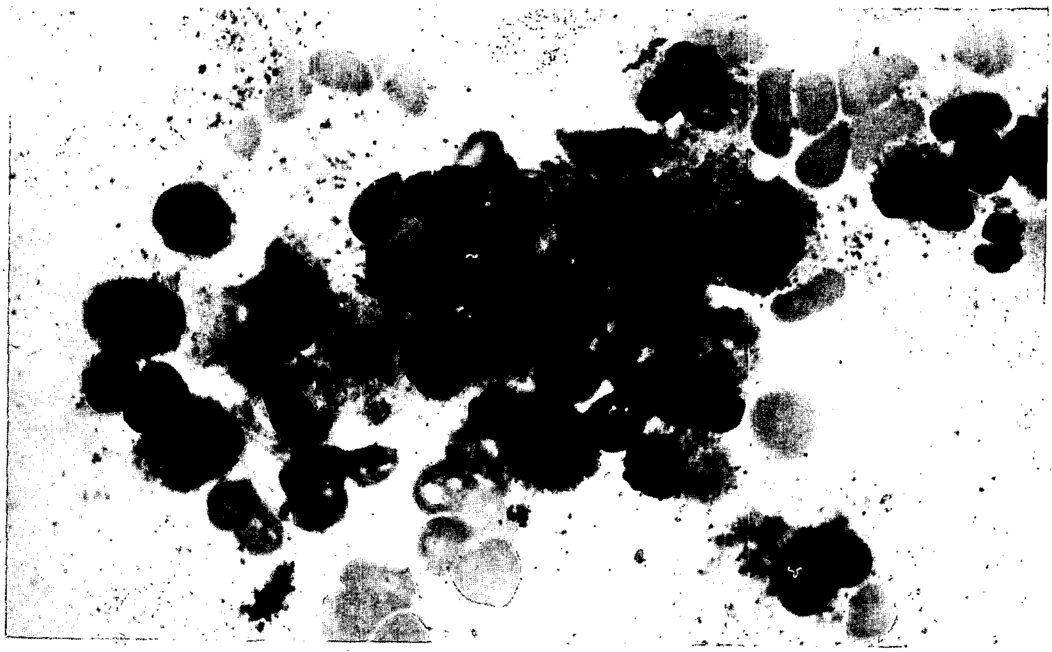


Fig. 55 (7)--Kijima. Autopsy Key # 50. Age 31. Male. 1000 meters. (See Fig. 52.) Imprint smear from another bone, same case as Figs. 52, 53, 54, showing myelocytes with the peculiar granules as well as abnormal lymphocytes and reticulum cells. X 1500. (Photo File # HM 313K; AMM Accession 158930-66.)

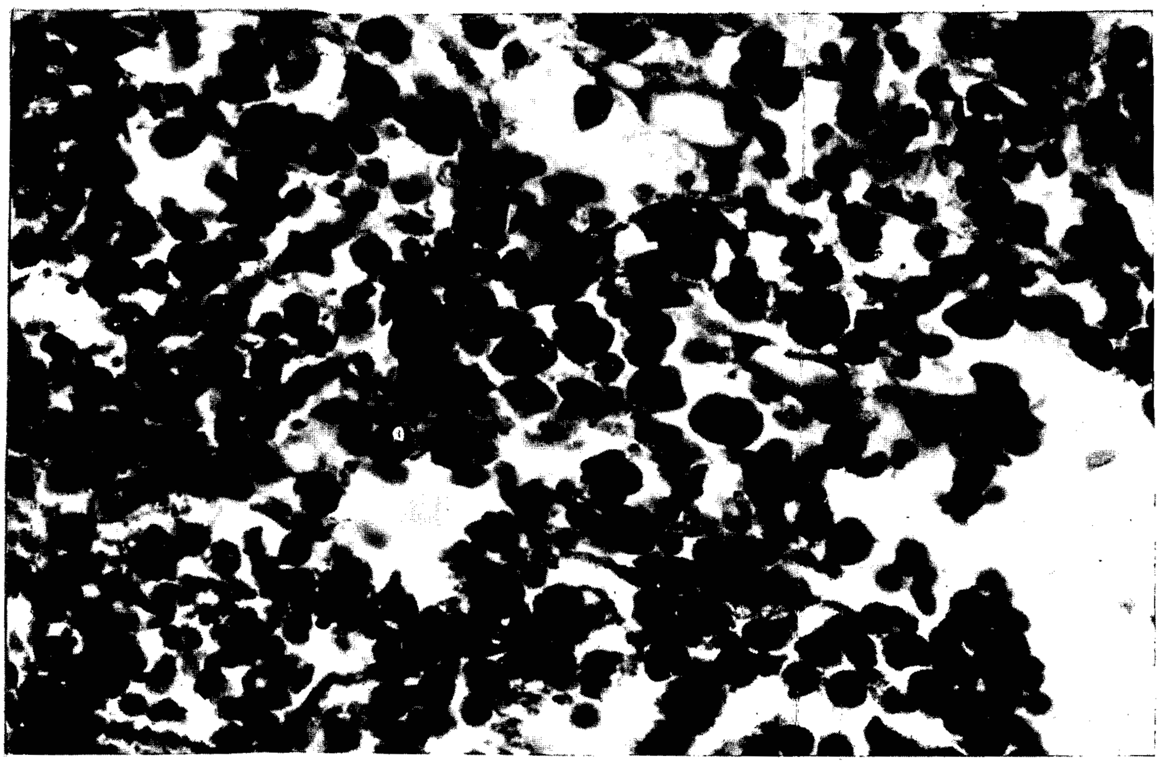


Fig. 56 (7)--Kijima. Autopsy Key # 50. Age 31. Male. 1000 meters. (See Fig. 52.) Section of vertebral marrow showing the mononuclear cells, some with granular cytoplasm, myelocytes, and others without. The appearance of the nucleus in many, with the single large nucleolus resembles that of young lymphocytes. Compare with Figs. 52, 53, 54, and 55. Giemsa, X 1200. (Photo File # HM 318K; AMM Accession 158930-66.)

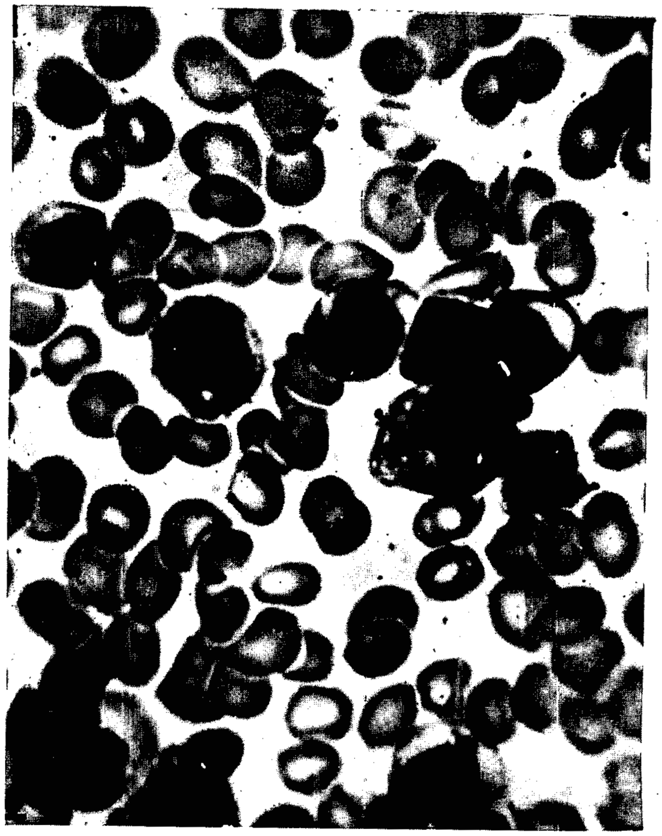


Fig. 57 (7)--Kobuke. Age 19. Female. 1300 meters. Sternal biopsy, 5 November 1945, showing several types of abnormal lymphocyte and an ordinary normoblast. X 1500. (Case S-9078-Ko.) (Photo File # HM 165K.)

Fig. 58 (7)--Kobuke. Age 19. Female. 1300 meters. (See Fig. 57.) Another field from smear, Fig. 57, showing more abnormal lymphocytes and two cells which suggest an affinity with reticulum cells. X 1500. (Case S-9078-Ko.) (Photo File # HM 166K.)

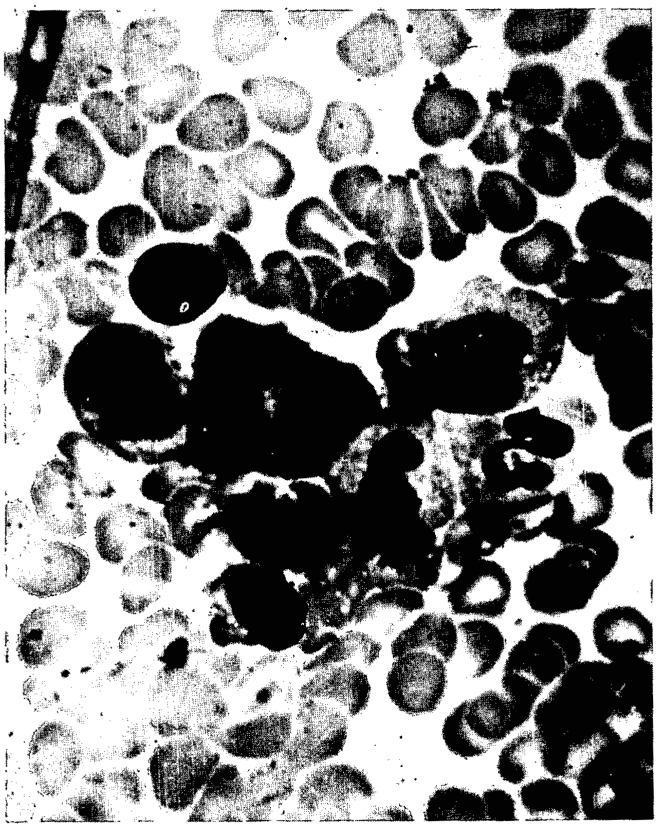


Fig. 59 (7)--Yoshioke. Age 18. Male. 1500 meters. Sternal biopsy, 29 October 1945, showing abnormal lymphocytes, small lymphocytes, and one very basophilic type, believed to be a plasma cell. X 1500. (Case No. H-6052-U.) (Photo File # HM 164K.)

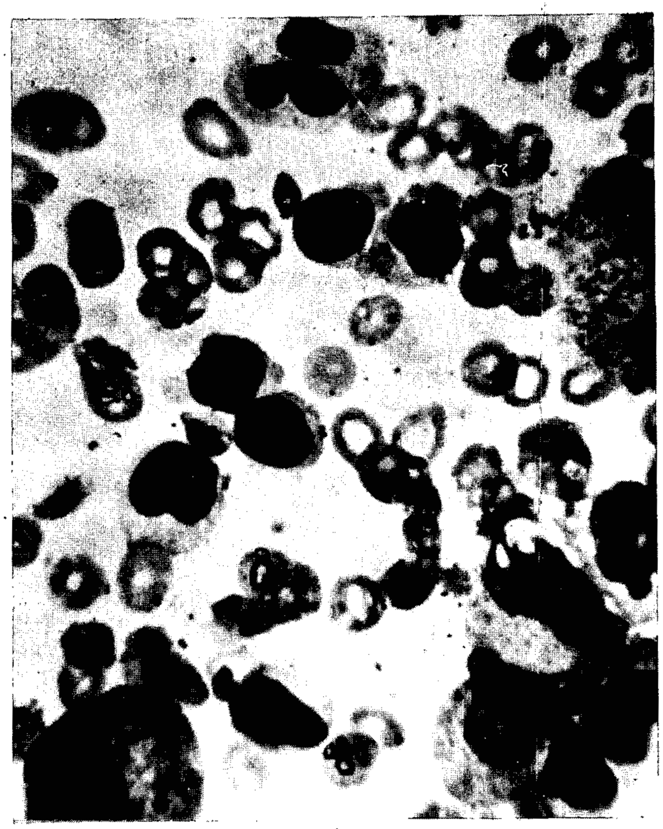


Fig. 60 (7)--Fujii. Age 28. Male. 500 meters. Sternal biopsy, 24 October 1945, showing ordinary small lymphocytes and a few abnormal types with large azurophile granules. X 1500. (Case H-6729-U.) (Photo File # HM 168K.)

Fig. 61 (7)--Fujii. Age 28. Male. 500 meters. (See Fig. 6.) Another field, same smear as Fig. 61, showing a blast-like cell with peculiarly large granules and a pair of abnormal lymphocytes. X 1500. (Case No. H-6729-U.) (Photo File # HM 167K.)

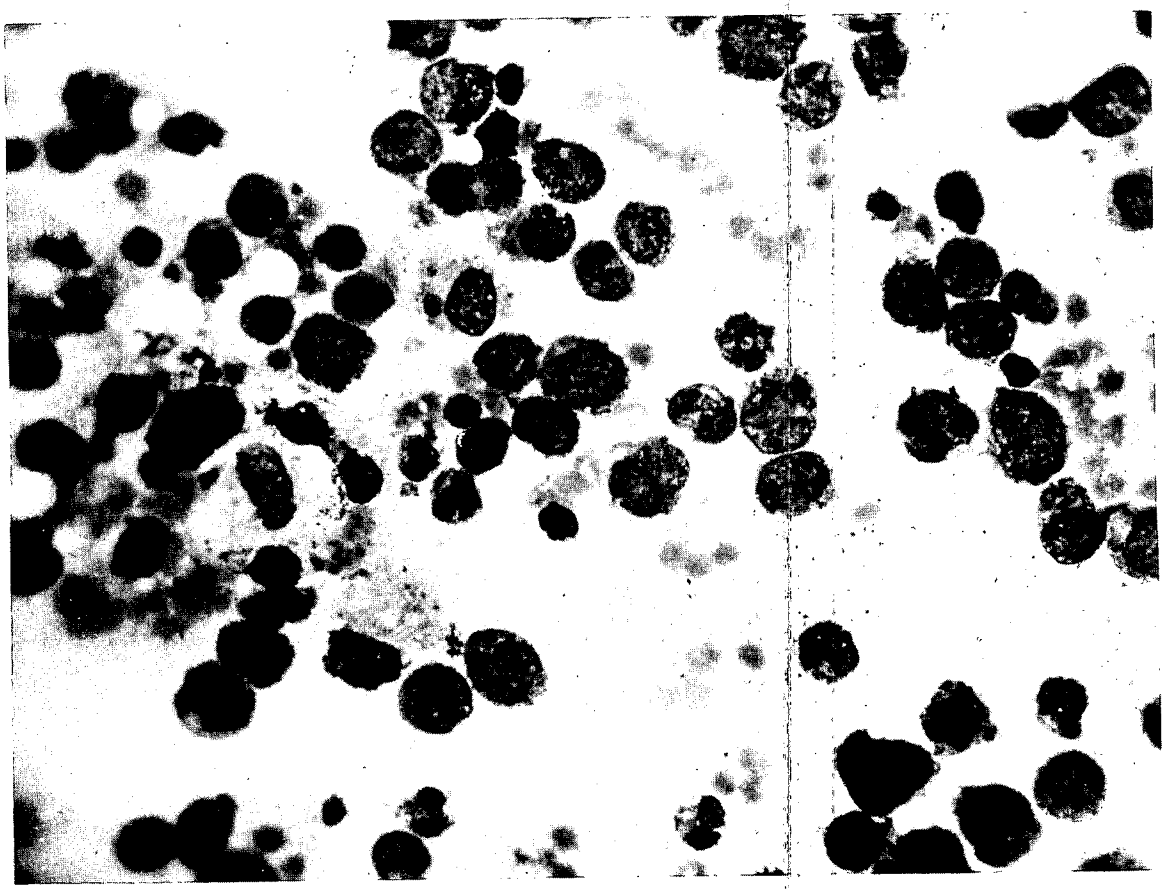


Fig. 62 (7)--Akiyama, Age 60. Female. 450 meters. Died 15 October 1945. Smear of sternal marrow showing many reticulum cells, some of which contain azurophile granules and resemble early myelocytes. X 1200. (Omura Naval Hospital Case No. 3098.) (Photo File # NM 153K; AMM Accession 158930-188.)

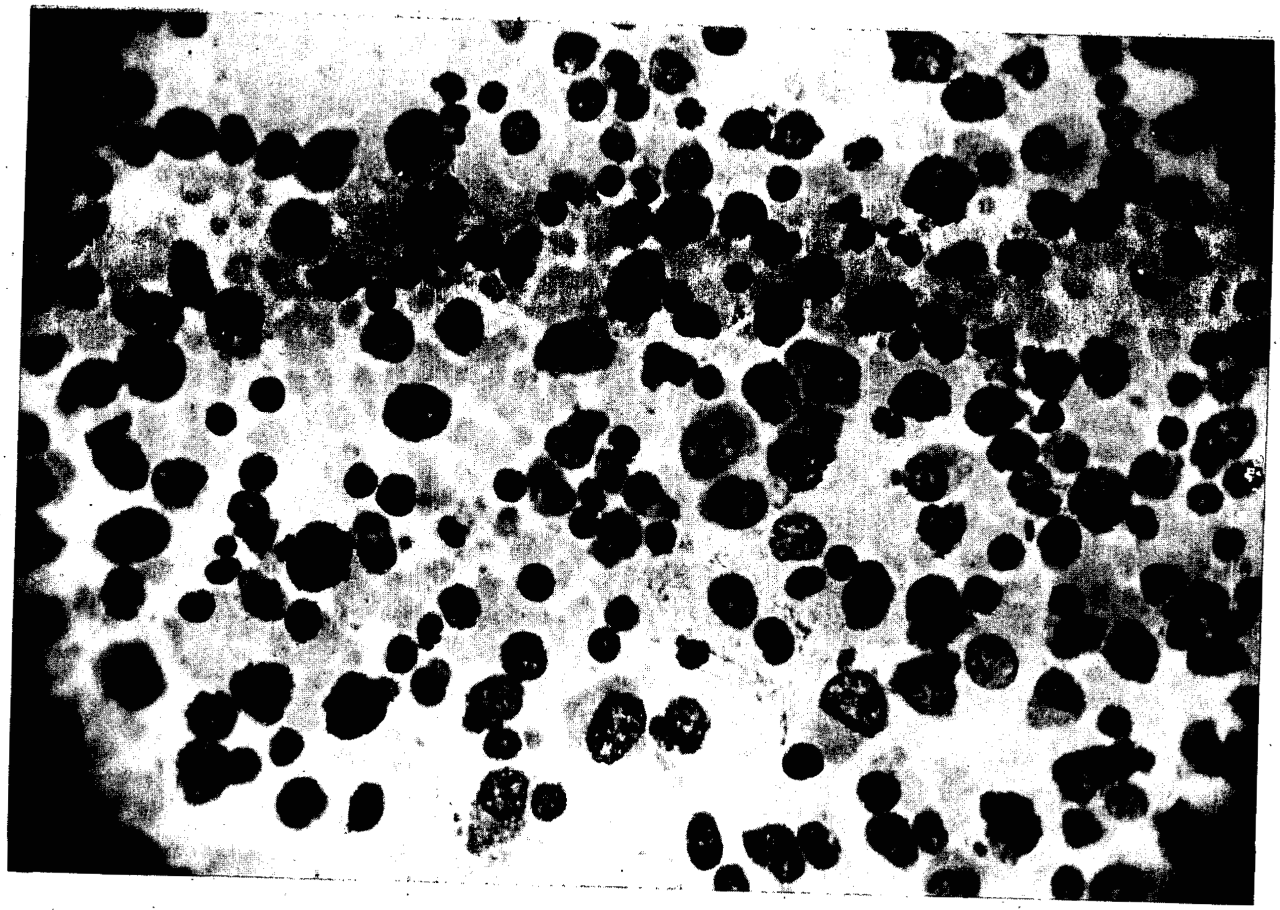


Fig. 63 (7)--Kisamatsu, Age 65. Male. 800 meters. Died 11 November 1945. Smear of sternal marrow showing reticulum cells, myelocytes, lymphocytes, and plasma cells. X 1200. (Omura Naval Hospital Case No. 3121.) (Photo File # NM 109K; AMM Accession 158930-188.)

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Armed Forces Institute of Pathology, Washington, D.C.
MEDICAL EFFECTS OF ATOMIC BOMBS - THE REPORT OF THE JOINT COMMISSION FOR THE INVESTIGATION OF THE EFFECTS OF THE ATOMIC BOMB IN JAPAN - VOLUME III, by Ashley W. Oughterson, George V. LeRoy, Averill A. Liebow, and others. 19 April '51, 213 pp. incl. photos, tables, graphs. UNCLASSIFIED

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