KYOTO UNIVERSITY

**HEMATOLOGICAL INVESTIGATION OF THE
ATOMIC BOMB SUFFERERS IN HIROSHIMA AND
NAGASAKI CITY**

By
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1952

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**Hematological Investigation of the Atomic Bomb
Sufferers in Hiroshima and Nagasaki City**

By

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Hematological investigation of the atomic bomb sufferers in Hiroshima and Nagasaki City.*

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Introduction

The clinical picture of the atomic bomb injuries has been reported in detail by KIKUCHI,¹⁾ one of the authors of this paper, at the Twelfth Congress of the Japanese Association of Medical Science, which was held in April, 1947. Furthermore atomic bomb injuries have been reviewed by TSUZUKI,²⁾ SASSA,³⁾ NAKAIZUMI,⁴⁾ KINOSHITA and MIYAKE⁵⁾ in the "Report on the Atomic Bomb Disasters" recently published by the Special Research Committee on the Atomic Bomb Disasters aided by the Scientific Research Council of the Japanese Educational Ministry.

In this paper we are going to describe the clinical picture of the acute and subacute radiation injuries caused by the atomic bomb from the hematological point of view, based upon the investigation of 1998 cases of atomic bomb sufferers observed by us (Table 1)⁶⁾ 107, 115, 407, 415, 437, 447 and 2850 case records presented to us from the authorities of many universities and hospitals at our request in 1947.

This report will also cover the sequelae of the atomic bomb injuries one and two years after the bombing.

Outlines of clinical picture

The influence of the atomic bomb on the human body may be divided into

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Table 1 Cases examined

City	Patients	Number of cases	Period of observation
Hiroshima	In-patients of the Ono Army Hospital	76	Sep. 5 — Sep. 17, 1945
	Out-patients of the Ono Army Hospital	140	Sep. 5 — Sep. 17, 1945
	Out-patients of the Ushida Clinic	645	Sep. 10 — Sep. 17, 1945
Nagasaki	In-patients of the Mitsubishi Hospital	26	Nov. 1 — Nov. 15, 1945
Hiroshima	Out-patients of circulating clinics	523	Aug. 19 — Sep. 10, 1946
Nagasaki	Out-patients of circulating clinics	172	Nov. 30 — Dec. 6, 1946
	Out-patients in Nishiyama area	173	Feb. 15 — Feb. 20, 1947
Hiroshima	Out-patients of circulating clinics	243	Oct. 10 — Oct. 19, 1947
Total		1998	

- (1) mechanical effects
- (2) effects due to heat and other rays
- (3) effects due to ionizing radiations.

Of these effects, the radiation effects are most characteristic of the atomic bomb injuries. Therefore we will discuss chiefly the atomic bomb injuries caused by the radiation effects, namely, atomic bomb radiation sickness, or in short, "radiation sickness". The symptoms of radiation sickness depend upon the doses of radiation received by individuals, which vary according to the distance from the bombing center and the efficiency of the shelter under which the individuals were placed. The closer to the bombing center the individuals were situated at the time of bombing, the higher the incidence of radiation sickness. Typical cases of radiation sickness were found chiefly within 2 km from the bombing center. There were also found, however, a few cases of radiation sickness even at a distance of 2 to 3 km from the bombing center.

Changes of peripheral blood

As the clinical picture of radiation sickness varies according to the stage of the disease, we will divide it into 4 stages given below:

- 1) The 1st stage From immediately after the bombing to the end of the 2. week — Acute symptoms
- 2) The 2nd stage From the 3. to 8. week — Subacute symptoms
Complications
- 3) The 3rd stage From the 3. to 4. month — Recovery stage

4) The 4th stage From the 5. month and on — Sequelae

Chronic symptoms

1) The 1st stage. Most of the sufferers complained of early symptoms such as general malaise, lassitude, nausea, vomiting and diarrhea. Although these complaints were more remarkable in those who have developed radiation sickness afterwards, they were also seen in many sufferers who did not show any particular symptom of radiation sickness. Those who were bombed very near the bombing center were for the most part killed immediately or died within the day of the bombing. Among the remainder there were also many cases which died from general emaciation within two or three days after the bombing in spite of slight burns or mechanical injuries. These patients are regarded to have suffered from the most severe radiation injuries. The details of the clinical and laboratory findings of these patients, however, are not available. Other patients complained of fever from 38° to 39°C beginning on the 3. or 4. day after the bombing accompanied by obstinate, sometimes bloody or mucous diarrhea, vomiting, hematemesis, hemoptysis, hematuria, etc., and died about ten days after the bombing. These patients are also regarded to have suffered from very severe radiation injuries. The details of the clinical and laboratory findings in these cases are also unknown. According to the report of the Kure Naval Station,⁶⁾ however, these patients already showed remarkable leukopenia within a week after the bombing. As given in Table 2, 7 cases out of 10 showed marked leukopenia ranging between 150 and 400 per cmm. In cases with marked leukopenia, the lymphocytes were reduced remarkably both in percentage and in absolute number. The neutrophils were also reduced remarkably in absolute number. In percentage, however, they showed relative neutrophilia, because the decrease of the lymphocytes was more remarkable than that of the neutrophils. Consequently the ratio of the neutrophils to the lymphocytes ($\frac{N}{L}$) was higher than normal (1.1-2.4), ranging between 3.9 and 10.8. The nuclear count of the neutrophils showed a marked shift to the left. Metamyelocytes were seen in most cases. The percentage of the eosinophils and monocytes were within the normal range even in the cases with marked leukopenia, although they were reduced in absolute number. The erythrocyte count and hemoglobin content were remarkably reduced in some cases. The decrease of the erythrocyte count and hemoglobin content, however, was generally not so remarkable as that of the leukocyte count. The color index was lowered in many

Table 2 Blood picture within 1 week after the bombing (Kure Naval Station)⁶⁾

Name	Erythro- cyte (×10000)	Hemo- globin %	Color index	Leuko- cyte	Differential count										Out- come	
					Baso- phils	Eosino- phils	Neutrophils					Lympho- cyte	Mono- cyte	Neutrophils		
							Myelo- cyte	Meta- myelocyte	Stab cells	Polymorpho- nuclears	Total			Lymphocytes		
O.	375	40	0.53	250	0	2	0	4	26	56	86 (215)	8 (20)	4	10.8		
F.	410	42	0.51	400	0	1	0	11	13	53	77 (308)	20 (80)	2	3.9	Fatal	
N.	420	50	0.59	150	0	2	0	9	8	66	83 (125)	13 (20)	2	6.4	Fatal	
K.	420	45	0.53	400	1	0	0	9	12	62	83 (332)	14 (56)	2	5.9	Fatal	
F.	265	32	0.60	400											Fatal	
Y.	184	23	0.62	340											Fatal	
O.	528	43	0.41	150	3	4	0	9	30	34	73 (110)	17 (26)	3	4.3	Fatal	
K.	300	49	0.81	4000	2	3	0	1	8	45	54 (2160)	36 (1440)	5	1.5		
K.	405	95	1.17	3080	1	4	0	0	10	48	58 (1663)	34 (1047)	3	1.7		
S.	330	65	0.98	3800	0	5	0	0	24	44	68 (2584)	22 (836)	5	3.1		
Normal	450—500	90—100	1.00	6000—8000	0—1	1—5	0	0	3—6	45—55	48—61 (2880—4880)	25—45 (1500—3600)	4—7	1.1—2.4		

() ; Absolute number

Fig. 1 Leukocyte count in the first week after the bombing

cases.

Fig. 1 shows the leukocyte counts in the first week after the bombing examined in 141 cases^{6) 7)}, which were exposed to the atomic bomb within 1.5 km from the bombing center. In 48.3 % of all cases examined, the leukocyte count was less than 5000 per cmm. There were not a few cases with leukopenia, which at that time had no subjective symptom and could continue military service as healthy individuals. Many of these apparently healthy individuals, however, developed a typical radiation sickness three or four weeks after the bombing.

2) The 2nd and 3rd stage.

Typical radiation sickness began as early as from five to six days, mostly about two weeks after the bombing with epilation, followed by fever, bleeding in the skin and mucous membrane, gingivitis, pharyngitis and diarrhea. Among these symptoms, fever, hemorrhagic tendencies, gingivitis and pharyngitis ran parallel with the hematological changes such as leukopenia and thrombocytopenia both in their severity and time of onset, indicating that there is a close relation between them.

The changes of the blood picture in this stage were examined in detail. We will explain the changes of the peripheral blood picture, dividing the cases into following 4 groups.

Group	Symptoms
I) Fatal cases	High fever, marked epilation, prominent hemorrhagic tendencies, necrotic gingivitis and tonsillitis, diarrhea.

II) Severe cases	High fever, marked epilation, hemorrhagic tendencies, gingivitis and pharyngitis.
III) Middle cases	Moderate fever, slight hemorrhagic tendencies, slight gingivitis and pharyngitis.
IV) Slight cases	Only one or two of the above mentioned symptoms.

1) Fatal cases (Fig. 2). The erythrocyte count and hemoglobin content were reduced considerably, becoming more and more remarkable with the lapse of time. The color index was higher than 1.0, and it showed especially a tendency to rise at the terminal stage of the disease. The reticulocyte count was decreased. The leukocyte count was reduced remarkably, showing the average value of 1100 per cmm three weeks after the bombing. There were not a few cases with the leukocyte count less than 500 per cmm.

The decrease of the neutrophils was especially pronounced. They were reduced remarkably not only in percentage but also in absolute number. The absolute number of the neutrophils was less than that of the lymphocytes. The lymphocytes were also reduced in absolute number. In percentage, however, they were increased because the decrease of the neutrophils outbalanced that of the lymphocytes. Consequently the ratio of the neutrophils to the lymphocytes ($\frac{N}{L}$) was remarkably lower than normal. The eosinophils were reduced or disappeared in most cases. Usually the basophils were not found. The monocytes were also decreased. Plasma cells appeared in many cases.

The leukocyte count showed a tendency to decrease progressively in most cases, although there were some cases, in which the leukocyte count showed a slight increase after reaching its lowest level. The platelets were also remarkably decreased, the count being less than 50,000 per cmm in most cases.

2) Severe cases (Fig. 3).

The erythrocyte count was markedly reduced, showing the average value of 2.825 million per cmm in the 4. week after the bombing. It decreased more and more until the 8. week, and then began to recover. In the 15. to 18. week, however, it was still below normal value, showing the average value of 4.1 million per cmm. The hemoglobin content was also decreased remarkably, averaging 59 % (Sahli) in the 4. week after the bombing. It decreased further until the 6. week, and thereafter it began to increase gradually. In the 15. to 18. week, however, it was not restored to normal,

Fig. 2 Peripheral blood picture (Fatal cases)

showing the average value of 86 % (Sahli). The color index had a tendency to rise, ranging between 1.1 and 1.3, during the stage when the erythrocyte count was decreasing. It returned to 1.0 as the erythrocyte count approached normal. The reticulocyte count

Fig. 3 Peripheral blood picture (Severe cases)

was reduced in the 4. week, averaging 1.3 ‰. After the 5. week it began to increase, reaching the highest level of 25.2 ‰ in the 7. week, and then it began to decrease with the increase of the erythrocyte count, showing the average value of 10 ‰ in the 10. week.

The platelet count was markedly reduced in the 4. week, being 32,000 per cmm in average. In the 5. week it recovered to 67,000 per cmm, and thereafter, it increased gradually. In the 11. to 14. week, however, it was still below normal level, showing the average

value of 168,000 per cmm.

The leukocyte count was remarkably reduced in the 4. week, being 1015 per cmm in average. In the 5. week, there was no sign of recovery in the leukocyte count. After the 6. week, however, the leukocyte count began to increase rapidly, and restored to normal in the 10. week, showing the average value of 7578 per cmm. In the 15. to 18. week it increased temporarily above normal (10425 per cmm in average) and returned to normal in the 19. to 22. week. As for the differential count, the neutrophils were markedly reduced in the 4. week. Its count was 304 per cmm in average, being less than that of the lymphocytes. In the 6. week, however, the count of the eosinophils showed the same number as that of the lymphocytes, and thereafter it increased in proportion to the increase of the total leukocyte count, reaching normal level in the 9. week. The lymphocytes were reduced to less than a half of the normal count in the 4. to 5. week, and thereafter they began to increase. The rate of their increase, however, was slow in most cases. The average count of the lymphocytes did not yet recover to the normal value (2100 per cmm) in the 10. week. It recovered to normal for the first time in the 15. to 18. week. When the lymphocytes were on the way to recovery, there was an increase of the immature lymphocytes with an increased number of mitochondria.⁹⁾

The eosinophils were decreased or disappeared in the 4. to 7. week. After the 8. week they began to increase, and after a temporary increase above normal in the 9. to 10. week, they returned to normal again. The basophils were usually not found. The monocytes were reduced in the 4. to 5. week. Thereafter they began to increase gradually, showing a tendency to increase above normal in the 15. to 18. week. The plasma cells were often increased in the 5. to 15. week, and thereafter they decreased gradually.

Fig. 3 shows the recovery rate of the granulocytes and lymphocytes in severe cases. At the acme of the disease, the ratio of the granulocytes to lymphocytes ($\frac{G}{L}$) was markedly lowered below normal. At the recovery stage, however, the increase of the granulocytes was rapider than that of the lymphocytes. Consequently the ratio of the granulocytes to lymphocytes returned relatively rapidly to normal, or temporarily even increased above normal.

The changes of the blood picture in middle and slight cases were the same in principle as in severe cases. The degree of the changes, however, was slighter, and the lowest level of the leukocyte count seemed to appear later in slight cases (Fig. 4).

Fig. 4 Changes of mean leukocyte count

Nuclear shift of the neutrophils (Fig. 5).

During the marked leukopenia in the 4. to 6. week, there was a remarkable shift to the left in the nuclear count of the neutrophils. With the recovery of the total leukocyte count, however, it approached gradually to the normal value. The immature leukocytes, younger than myelocytes, were rare even at the stage with a marked shift to the left of the nuclear count. It was reported that the immature leukocytes such as promyelocytes and myeloblasts appeared in a few cases. In our investigation, however, we could not observe such cases.

Morphological and functional changes of leukocytes (Fig. 6). During the acme of leukopenia, there were various degenerative changes of leukocytes such as vacuolation, toxic granulation, pyknosis of nuclei, poor staining, swelling of nuclei and the like. The neutrophils appeared to become much larger than usual, and the mean diameter of the neutrophils was increased in severe cases.

The phagocytic activity of the neutrophils, tested with Indian ink forty-six to seventy-six days after the bombing, was lowered not only in the cases with leukopenia, but also in the cases with

Fig. 5 Nuclear shift of neutrophils

Fig. 6 Phagocytic function and peroxidase reaction of neutrophils

normal or increased leukocyte count. This result may be considered to show that the functions of leukocytes were not restored to normal even after the leukocyte count had returned to normal.⁹⁾ The peroxidase reaction of the neutrophils was also decreased.⁹⁾

Morphological changes of erythrocytes (Fig. 7).

In the 3. to 6. week after the bombing, the more severe the cases were, the more remarkable was the anisocytosis. It was found in 62 % to 40 % of fatal cases, and in 44 % to 46 % of severe cases. With the recovery of anemia, however, the anisocytosis became less prominent. Poikilocytosis was not pronounced. In severe cases, it

Fig. 7 Morphological changes of erythrocyte

was found in 4.4 % in the 3. to 4. week, in 16.3 % in the 7. to 8. week, and thereafter it decreased in percentage. In middle and slight cases it disappeared in the 5. to 8. week, namely earlier than in severe cases. Polychromasia and basophilic stippling were also not so pronounced. In the 3. to 4. week, they were observed in higher percentage in middle and slight cases than in fatal and severe cases. Thereafter they became less prominent in middle and

Table 3 Diameter of erythrocyte

Date of examination Mean diameter (μ)	September, 1945		September, 1946	
	Number of cases	%	Number of cases	%
Over 9.0	2	5.8	0	0
8.9 — 8.5	2	5.8	0	0
8.4 — 8.0	11	32.3	0	0
7.9 — 7.5	15	44.5	31	62
7.4 — 7.0	4	11.6	19	38
under 6.9	0	0	0	0

Date of examination Diameter	September, 1945	September, 1946
Mean diameter	7.968 μ (34 cases)	7.572 μ (50 cases)
Max. mean diameter	9.442 μ	7.915 μ
Max. diameter	12.5 μ	10.0 μ

Fig. attached to Table 3 Diameter of erythrocyte
(Price-Jones curve)

slight cases, while in severe cases, they became more prominent with the lapse of time, reaching the acme in the 7. to 8. week, and then decreased in their degree with the recovery of anemia. Normoblasts were found in some cases. They appeared more frequently in severe cases than in middle and slight cases. They were most frequently found in the 7. to 8. week. The diameter of erythrocyte was usually enlarged. The mean diameter of erythrocyte of 34 cases examined in the 4. to 6. week was 7.968μ in average, the largest

Fig. 8 Morphological changes of platelets

mean diameter being 9.442μ (Table 3 and attached figure).

Platelets. The decrease of the platelet count was remarkable in proportion to the severity of the disease. Morphologically observed, all the small, middle and large types of platelets were decreased, especially the decrease of the small and middle type was remarkable (Fig. 8). They showed degenerative changes such as poor staining, diminution of Azur granules and the like. At the recovery stage, the platelet count increased temporarily above normal in some cases.

Hemorrhagic diathesis. Hemorrhagic diathesis was one of the most important symptoms of radiation sickness. Hemorrhages were observed more frequently in severe cases, and most frequently in the skin. Bleeding from the gums was also observed in many cases. Epistaxis, hematemesis, hemoptysis, bloody diarrhea, hematuria and bleeding from the uterus were seen in some cases. The hemorrhagic tendencies appeared in most cases in the 3. to 6. week concurrently with fever or a little later than the fever. There was a close relation between the reduction of the platelet count and the appearance of hemorrhagic tendencies. As shown in Fig. 9, the more marked the thrombocytopenia was, the more frequently the hemorrhagic tendencies were observed.

Fig. 9 Relation between hemorrhagic symptoms and platelet count

The bleeding time was remarkably prolonged in severe cases. As shown in Fig. 10, the prolongation of the bleeding time was observed in cases with the platelet count less than 100,000 per cmm, and the bleeding time became longer in proportion to the decrease of the platelet count. With the recovery of the platelet count, the prolongation of the bleeding time became less prominent, and it returned to normal in

the 9. week even in severe cases. The agglutinative and retractile functions of platelets were markedly lowered in severe cases.¹⁰⁾ The thrombi-formation time was remarkably prolonged

in severe cases. The coagulation time was moderately prolonged in severe cases, while it was usually normal in middle and slight cases.¹⁰⁾ The plasma prothrombin was decreased moderately in severe cases, while in slight cases it was normal or only slightly decreased. The Rumpel-Leede's phenomenon was moderately positive in severe cases.¹⁰⁾ The resistance of capillary wall, tested by means of the Borbely's method, was lowered only in a few cases. From the laboratory findings mentioned above, the main cause of the hemorrhagic diathesis in radiation sickness should be ascribed to the reduction of the platelet count. However, the other factors, such as disturbance of blood clotting, lowered resistance of blood capillaries, etc. must not be neglected.

Fig. 10 Relation between bleeding time and platelet count

The resistance of erythrocyte against hyposmotic salt solution showed usually no remarkable change, although in a few cases decrease of the minimum resistance or the maximum resistance was observed.

The sedimentation rate of erythrocyte was remarkably accelerated in severe cases. There was generally a parallelism between the degree of leukopenia on one side and the degree of the acceleration of sedimentation rate, prolongation of bleeding time and the decrease of the erythrocyte count on the other. There were, however, not a few cases with the leukocyte count less than 4000 per cmm, in which the sedimentation rate, bleeding time and erythrocyte count were in the normal range. Therefore as an indicator for radiation injuries, the leukocyte count seems to be most useful.¹⁰⁾

Relation between the leukocyte count, sedimentation rate and bleeding time on one side and the distance from the bombing center on the other (Fig. 11).

We made a mass examination about 617 cases in Hiroshima City from September 10. to September 16., 1945, namely 6 weeks after the

Fig. 11 Relation between the leukocyte count, sedimentation rate, bleeding time and the distance from the bombing center

bombing. The average leukocyte count of 617 cases was 6025 per cmm, and the closer the individuals were to the bombing center at the time of explosion, the more remarkable was the reduction of the average leukocyte count. There were not a few cases showing leukopenia without any subjective or objective symptom.

As shown in Fig. 11, the average value of the sedimentation rate was accelerated in inverse proportion to the distance from the bombing center, and the average value of the bleeding time was more markedly prolonged in inverse proportion to the bombing center.

Bacteriological examination of blood. At the acme of radiation sickness showing sepsis-like symptoms such as high fever, hemorrhagic tendencies, necrotic gingivitis and tonsillitis, pyogenic bacteria (hemolytic streptococcus, streptococcus viridans, staphylococcus and colon bacillus) were cultivated from the blood in not a few cases. Judging from this result, at least some severe cases should be considered to have been complicated by sepsis.

Changes of bone marrow picture.

In severe cases the number of nucleated cells were markedly reduced, ranging from 5000 to 20,000 per cmm at the acme of the

disease. The erythropoietic function was greatly disturbed. The immature cells such as proerythroblasts, basophilic macroblasts and basophilic normoblasts were especially very scarce or had almost disappeared. In the leukopoietic series, the neutrophils were remarkably decreased. Especially the decrease of the immature forms such as promyelocytes and myelocytes was pronounced (Fig. 12).

Fig. 12 Bone marrow picture

There remained chiefly the mature cells such as metamyelocytes, stab cells and polymorphonuclears. The eosinophils were also reduced or disappeared. In the granulocytes there were observed, as in the peripheral blood, various degenerative changes such as vacuolation, toxic granules, pyknosis or obscure structure of nuclei, increase of nuclear shadow and the like. Contrary to the decrease of the

granulocytes, the lymphocytes were increased in percentage. The monocytes, plasma cells and reticulum cells were also often increased in percentage.

The megakaryocytes were markedly decreased. The megakaryocytes which were found were mostly of the mature or transitional type. The immature types such as promegakaryocyte and megakaryoblast were very rare. Sometimes masses of protoplasm without nuclei or naked nuclei were seen. The megakaryocytes showed often vacuolation. Their nuclei were sometimes distorted, and the thrombopoietic function was markedly impaired.

In middle cases on the way to recovery the percentage of the erythropoietic series was normal or increased above normal, and the proerythroblasts, basophilic and polychromatic macroblasts as well as normoblasts were found in sufficient number. In the leukopoietic series, the percentage of the neutrophils was almost normal or only slightly decreased, and there were found not only the polymorphonuclears and stab cells but also the metamyelocytes and promyelocytes in sufficient number. These findings show that both the erythropoietic and leukopoietic function of the bone marrow were on the way to recovery. The eosinophils, which were decreased in the acme of the disease, were found increased with the recovery of the leukopoietic function. The increase of the percentage of the lymphocytes was less pronounced. The decrease of the megakaryocytes was also less prominent. The immature types of megakaryocytes appeared, and the thrombopoietic function was on the way to recovery. In short, the bone marrow function was markedly injured in severe cases. The immature forms of both the erythropoietic and leukopoietic series were especially injured severely. The thrombopoietic series were also injured. These changes of the bone marrow seemed to precede the changes of the peripheral blood picture, as revealed by the follow-up examination of the sternal bone marrow and the peripheral blood.

Etiological considerations.

The ionizing radiations produced by the explosion of the atomic bomb may be classified as follows : ⁴⁾

- 1) High energy γ -rays and neutrons released by the chain reaction.
- 2) γ -rays originating in capture reactions.
- 3) Neutron-induced radioactivity produced in the matters on the ground and tissues of the human body.

4) Fission products formed in the chain reaction.

Among these ionizing radiations, 1) and 2) are regarded as the main cause of radiation sickness. According to the report of the Pathological Institute of Kyoto University¹²⁾ and others¹³⁾, however, induced radioactivity was found in the bones and other various tissues of the patients who died of radiation sickness. How much influence this induced radioactivity exerted upon the development of radiation sickness is not known. Some researches¹²⁾, however, stated the opinion that the induced radioactivity, especially that of radiophosphorus produced in the body by the reaction $^{31}_{15}\text{P} + {}^1_0\text{n} \rightarrow ^{32}_{15}\text{P}$, might have had some influence upon the hematopoietic organs in the fatal cases which were bombed at a distance very close to the bombing center.

Be that as it may, the effects of the ionizing radiations mentioned above upon the human body are regarded identical in principle as the effects of X-rays^{14), 15), 16), 17), 18), 19), 20), 21), 48)}, and it has long been known that the most sensitive organs to these ionizing radiations are the hematopoietic organs, the gastrointestinal tract, the hair follicles and the gonads.^{16), 18), 20)} Therefore the observation of the effects of large doses of X-ray irradiation upon animals will contribute to the understanding of the symptoms of radiation sickness caused by the atomic bomb. Fig. 13 shows the changes of the peripheral blood picture of a rabbit exposed to a large dose (3000 r) of X-rays.²²⁾ As shown in the figure, the lymphocytes decreased remarkably immediately after the irradiation. The heterophils also decreased markedly, after showing a temporary increase following the irradiation. The eosinophils also decreased. The plasma cells were frequently observed. The erythrocyte count decreased. The decrease of the erythrocyte count, however, was not so remarkable as that of the leukocyte count. The reticulocyte almost disappeared two days after the irradiation. The platelet count began to decrease a little later than the leukocyte count. The phagocytic and migrating functions of the heterophils were lowered.

These changes of the peripheral blood picture are identical with those in radiation sickness caused by the atomic bomb. From the results of the study of bone marrow pictures in man and animals exposed to the atomic bomb^{1), 3), 10), 12)}, as well as from the results of the pathological and histological examination of their hematopoietic organs^{5), 12), 20), 23), 24), 25)}, it is evident that these changes of the peripheral blood picture as mentioned above were caused by the injuries of the hematopoietic organs such as the bone marrow, spleen and lymph

Fig. 13 Influence of large dose X-ray irradiation upon the blood picture of rabbit (Nishikawa)

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nodes. In short, these changes may be called "panhematophthisis." Necrotic gingivitis or pharyngitis, which is one of the most important symptoms of radiation sickness, may be attributed to the secondary bacterial infection due to the lowered resistance as a result of the reduction of leukocytes. Hemorrhagic diathesis, which is also one of the most important symptoms of radiation sickness, may be considered to have been caused chiefly by the reduction of the platelet count. Therefore it seems not too much to say that the clinical picture of the atomic bomb radiation sickness is based on the injury of the hematopoietic organs caused by the ionizing radiation of the atomic bomb.

The other important symptoms of radiation sickness such as epilation, diarrhea and disturbance of the sexual function may be well understood from the sensitivity of the organs to radiation. Furthermore the toxemia caused by tissue destruction and bacterial infection, functional disturbance of various organs, diarrhea and vomiting due to injuries of the gastrointestinal tract, loss of body fluid and disturbance of nutrition and acid-base balance may be considered to have had great influence upon the course and prognosis of radiation sickness. The early symptoms such as nausea, vomiting, general malaise and diarrhea, which occurred immediately after the bombing have long been well known in radiologists as an effect of radiation.

Course and prognosis

According to the statistics made by Masuyama,²⁾ 99 % of the deaths caused by the atomic bomb occurred within forty days after the bombing. Most of the deaths which occurred on the day of the bombing or within a few days after the bombing were caused by severe mechanical injuries, burns, or radiation sickness or combination of two or three types of these injuries. The deaths after two or three weeks following the bombing, however, were caused chiefly by radiation sickness, especially by the destruction of hematopoietic organs accompanied by secondary bacterial infection. After three months following the bombing, bacterial infections such as pneumonia, gangrene of the lung and sepsis, malnutrition, and in some cases aplastic anemia were listed as the cause of death. It must also be noted that leukemia, though rare in number, was reported as the cause of death at this stage.^{26) 27)}

As for the relation between the changes of blood picture and the prognosis of radiation sickness, the more remarkable the leukopenia,

anemia and thrombocytopenia were, the more unfavourable was the prognosis. Those who showed a leukocyte count less than 1000 per cmm had usually unfavourable prognosis, although there were not a few cases which recovered from a leukocyte count less than 1000 per cmm. At an early stage, there was no relation between the count of eosinophils and prognosis. Three to four weeks after the bombing, when the typical radiation sickness developed, however, the disappearance of the eosinophils showed an unfavourable prognosis, and the reappearance or increase of the eosinophils showed a favourable prognosis. The increase of the monocytes was also regarded as a sign of good prognosis.

The relation between burns and radiation sickness.

Some researchers declared that burns had some favourable influence upon radiation sickness. According to the report of the Research Corps of Tokyo University,³⁾ petechiae were found less frequently in cases with burns than in those without burns in the area beyond 2 km from the bombing center in Nagasaki City, indicating that burns had an suppressing effect upon the appearance of petechiae.

Changes of the blood picture as related to the course of radiation sickness.

From the results of the observation mentioned above, it may be concluded that the changes of the blood picture following exposure to the atomic bomb appeared at first in leukocytes. The decrease of the leukocyte count, especially that of the lymphocytes, was observed already at the early stage. The decrease of the granulocytes began a little later than that of the lymphocyte. Whether or not there was an initial granulocytosis immediately after the bombing is not known. The decrease of the platelet count appeared a little later than that of the leukocyte, and the decrease of the erythrocyte count was observed a little later than that of the platelet. At the recovery stage, the leukocyte increased rapidly in number. The increase of the granulocytes was especially rapid. The eosinophils were frequently increased. Contrary to the rapid increase of the granulocytes, the recovery of the lymphocytes was usually slow, and there were not a few cases in which the lymphocyte count was not restored to normal even after ten weeks following the bombing. The recovery of the platelet and erythrocyte count seemed to have been delayed as compared with that of the leukocyte. At the recovery stage, there were some cases which showed a temporary leukocytosis or fluctuation of the leukocyte count. In a few cases the

recovery of the leukocyte count was extremely delayed.

These changes of the peripheral blood picture were the same as those observed in animals exposed to radiation, and well understandable from the histological changes of the hematopoietic organs of these animals and of the patients who died from radiation sickness.

Treatment.

From the pathogenesis of radiation sickness as mentioned above, the main objectives in the treatment of the patients are ; ^{28) 30)}

- 1) to maintain adequate fluid and acid-base balance
- 2) to eliminate toxic substances from the body
- 3) to control infectious processes
- 4) to combat the hemorrhagic phenomena and
- 5) to stimulate the hematopoietic function.

For the purpose of 1) and 2) injections of glucose, fructose, physiologic salt solution, Ringer's solution, vitamin B, C, and transfusion of whole blood or dry plasma were used. Penicillin was effective to control the infections.³¹⁾ Streptomycin,³¹⁾ aureomycin³²⁾ and other antibiotics would also be effective. To combat the hemorrhagic phenomena, local treatment as well as blood transfusion and injections of vitamin K, P, C, calcium and various blood coagulants were tried. Recently it has been reported that protamine sulfate and toluidine blue are effective to control the hyperheparinemia, which is presumed as one of the causes of the hemorrhagic tendencies in radiation sickness. Rutin may be used for increased permeability of blood capillaries. For the purpose of stimulating the hematopoietic function, blood transfusion, intrasternal blood transfusion, autotransfusion, crude liver, liver preparations, gastric mucosa of swine, bone marrow preparations, reduced iron, nucleinacidic sodium, vaccine, omnadine and moxibustion were tried. Among these therapeutic procedures and medicaments repeated blood transfusion and liver preparations were reported to be effective. We also confirmed the effectiveness of blood transfusion in cases with marked leukopenia less than 1000 per cmm.

Folic acid, vitamin B₁₂ and cysteine may be also indicated to stimulate the hematopoietic function. Hormones of the adrenal cortex and pituitary gland were used in some cases, and it was reported that the former had a favourable influence upon radiation sickness.³³⁾ We tried further preparations of the parathyroid gland, calcium carbonate and phosphorus containing medicaments to accelerate the excretion of radioactive substances from the body. The

observation term, however, was too short to confirm their effect. Needless to say, that rest, sufficient nutrition and symptomatic treatment were necessary for the rapid recovery of radiation sickness.

Prophylaxis. Adequate shelter such as lead, iron and concrete will be useful to protect the ionizing radiations produced by the explosion of the atomic bomb. Recently it was reported that cysteine^{25), 26)}, glutathione^{26), 27)} and ACTH²⁸⁾, administered one hour before the irradiation, was effective to alleviate radiation sickness.

Influence of the residual radiation.

- 1) Examination of the leukocyte count of those who entered Hiroshima City soon after the bombing.

Among 20 persons who were far away from Hiroshima City at the time of bombing, but entered there soon after the bombing and engaged in the disposal of corpses and cleaning up of debris near the bombing center, we found 3 cases with the leukocyte count from 2000 to 3000 per cmm, and one with the leukocyte count from 3000 to 4000 per cmm.¹⁰⁾ Putting together various reports, we could find leukopenia less than 5000 per cmm in 32.3 % of 62 persons who entered Hiroshima City within one week after the bombing. It will be too much to say that all of these leukopenias were caused by the residual radiation. It could not be denied, however, that the residual radiation had some influence upon the human body soon after the bombing, although there was no case in which the injury was so severe as to result in death.

- 2) Influence of the fission products.

An area, called „Nishiyama“ in Nagasaki City, was protected from the direct radiation effect of the atomic bomb, because this area was behind Mt. Kompira on the opposite side of the bombing center. By fallen fission products, however, radioactivity about 200 to 300 times as strong as the natural radioactivity was found in this area at the investigation on October 1, 1945, and several radioisotopes such as Sr⁹⁰, Ba¹⁴⁰, Ce¹⁴⁴, Zr⁹⁵ and Pr¹⁴⁴ were discovered in the soils of this area.⁹⁾ According to the examination made by the member of the Radiological Department of Kyushu University, most of the people in this area showed a leukocytosis fifty to eighty days after the bombing. The leukocytosis reached from 30,000 to 50,000 per cmm in some cases. At the first examination on October 1, 1945, the leukocytosis was most frequently seen in children, and next to them it was frequently observed in young and middle-aged persons,

while aged persons above fifty years showed no leukocytosis. At the second examination in January 1946, namely five months after the bombing, leukocytosis was also observed in aged persons, while in children leukocytosis was found less frequently as compared with the result of the first examination.

In our investigation in November, 1946,⁴⁰ we could confirm in Nishiyama area radioactivity 5 to 30 times as strong as the natural radioactivity. The leukocytosis seemed to be declining, showing its acme in January or April, 1946. At the examination in February, 1947, however, there were still not a few cases with leukocytosis in this area.⁴⁰ The leukocytosis was found in 51 % of the examined persons. As for the differential count, slight eosinophilia, shift to the left of the neutrophils and sometimes a small number of metamyelocytes were found. The immature cells younger than metamyelocytes were not observed. Slight polycythemia (more than 5.5 million per cmm) was found in 10 % of the examined cases. There was no change in the reticulocyte and platelet count. The leukocytosis was found even in the residents who came to this area after the bombing, and it is supposed to have been caused by the weak, but long lasting residual radiation in this area. The changes of the blood picture of the people in Nishiyama area seem to need further investigation, because it has as yet not been confirmed in radiology that permanent leukocytosis can be caused by a primary stimulating effect of radiation.^{15) 17) 19)}

Effects of the atomic bomb one year after the bombing.

We examined 523 cases of the atomic bomb sufferers in Hiroshima City from August 19. to September 10, 1946, and compared the result with that of the control (173 healthy individuals in Hiroshima City, who did not encounter the atomic bomb explosion).⁴¹ Among the atomic bomb sufferers, there were many cases which complained of general malaise, vertigo and palpitation even one year after the bombing, and in a few cases hemorrhagic diathesis was observed. As for the blood picture, decrease of the erythrocyte count, elevation of the color index, decrease of the leukocyte and platelet count were more frequently seen in the atomic bomb sufferers than in the control. These differences were statistically significant. SNELL, NEEL and ISHIBASHI⁴² have also reported that the erythrocyte count, hemoglobin concentration, hematocrit reading and lymphocyte count were slightly, but significantly depressed in the atomic bomb sufferers in Hiroshima City twenty to thirty-three months after the bombing as compared with the control in Kure City, which is located

Fig. 14 Erythrocyte count one and two years after the bombing

Fig. 15 Color index one and two years after the bombing

18 miles from Hiroshima City.

In our investigation of sternal bone marrow, there were some atomic bomb sufferers with impaired bone marrow function. The phagocytic activity of the neutrophils was still lowered in some cases, but there were also some cases with normal phagocytic

Fig. 16 Leukocyte count one and two years after the bombing

Fig. 17 Platelet count one and two years after the bombing

activity in spite of leukopenia. The migrating function of the neutrophils was generally lowered as compared with the control. The relation between the migrating function and the leukocyte count was indefinite.

We also examined 172 cases of the atomic bomb sufferers in Nagasaki City from November 30. to December 6, 1946, and compared the result with that of the control (45 healthy individuals in Nagasaki City who did not encounter the atomic bomb explosion).⁴³⁾ Among the atomic bomb sufferers there were not a few cases with anemia, leukopenia and thrombocytopenia. These changes, however, were not statistically significant as compared with the control.

Effect of the atomic bomb two years after the bombing.

We examined 243 cases of the atomic bomb sufferers in Hiroshima City from October 10. to October 19, 1947, namely two years and two months after the bombing.⁴⁴⁾ There were not a few cases which complained of general malaise, vertigo and palpitation, although these complaints were not so frequent as in the previous year. Hemorrhagic diathesis was also observed in few cases. There were some cases with anemia, leukopenia, thrombocytopenia, prolonged bleeding time and impaired bone marrow function. These changes, however, were less frequent, and the phagocytic and migrating functions of the neutrophils were also less impaired as compared with the previous year. From these results it may be concluded that the blood cells of the atomic bomb sufferers were on the way to recovery both quantitatively and functionally.

Summary and conclusion

Based upon the results of our investigation on the atomic bomb sufferers in Hiroshima and Nagasaki City, we described the acute and subacute radiation injuries caused by the atomic bomb as well as the influence of the atomic bomb one and two years after the bombing from the hematological point of view. Although the blood pictures of the atomic bomb sufferers were almost restored to normal two years after the bombing, there were still some cases with impaired hematopoietic functions. Furthermore it cannot be assured that the hematopoietic organs of those who have seemingly recovered from the atomic bomb injuries can meet the great demand just in the same manner as healthy individuals, when they are exposed to profound injuries, such as severe infection, large hemorrhage, serious intoxication and the like.

It is also noted from the experiences in radiologists and animal experiments that leukemia can be provoked by radiation,^{45) 46) 47)} and actually it is reported that the incidence of leukemia in the atomic bomb sufferers in Hiroshima City is higher than that of the control.⁴⁸⁾

Therefore we deem it necessary to observe the blood picture of the atomic bomb sufferers for a long time in future.

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