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HEMATOLOGICAL EFFECTS ON HEAVILY IRRADIATED JAPANESE FISHERMEN

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INTRODUCTION

On 1 March in 1954, a thermonuclear test explosion was performed by the United States Authorities at Bikini Lagoon in the Pacific Ocean. At that time one Japanese fishing boat "the 5th Fukuryu-maru" was located at about 90 miles east from explosion center. The boat was nearly 100 tons and 23 fishermen aged from 18 to 39 were on board.

At about 3 : 40 a. m., while they were occupied in fishing tuna they saw a huge red light in the west and heard a detonation several minutes later. At about 7 : 00 a. m. white material began to fall, which continued for approximately 5 hours. They gave up fishing and returned to their mother port on 14 March 1954.

After landing, all the fishermen were found to have been injured by the radioactive materials. Seven of them were hospitalized to the Tokyo University Hospital and the other 16 were received by the First National Hospital of Tokyo by 28 March. They were discharged from both hospitals in May 1955, except for one fatal case who died on 23 September 1954. After being discharged we continued the follow-up studies so far as possible on annual basis. However, mainly because of the varied status of their occupations and widely distributed addresses, it was not always possible to get them all together for medical examination.

Medical data of the fishermen have been reported several times (MIYOSHI and KUMATORI, 1955; KOYAMA et al., 1955; MIKAMO et al., 1956; MIYOSHI and KUMATORI, 1962; KUMATORI and MIYOSHI, 1963; MIYOSHI and KUMATORI, 1964; KUMATORI et al., 1965).

FALLING OF RADIOACTIVE MATERIALS

During the falling of the white materials, when its intensity was greatest, these persons were unable to keep their mouths and eyes open. Their footprints were clearly marked on the deck covered by fallout.

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(2) Externally from th
the deck etc.
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Subject No.
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T-3
T-5
T-6
T-7
T-8
K-1
K-2
K-3
K-4
K-5
K-6
K-7
K-8
K-9
K-10
K-11
K-12
K-13
K-14
K-15
K-16

* T-3 put the fall-out n
added in total.

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ERIALS

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STATE OF IRRADIATION AND ESTIMATED RADIATION DOSE

The fishermen were irradiated in the following 3 ways:

(1) From the radioactive materials adhering to the body surface.
(2) Externally from the radioactive materials deposited in the cabins, on the deck etc.
(3) Internally from the radioactive materials entering various organs.

The diameters of the fallout materials, which were the powders of coral-reef fragments, ranged from 19 to 460 μ, mainly 100 to 400 μ (KIKUCHI et al., 1954). According to the results of radiochemical analysis of fallout on 26 March, rare-earth elements contributed about 50 per cent of the total radio-activity and uranium contributed about 20 per cent (KIMURA et al., 1956). The specific activity of the material was 0.37 mCi/g on 23 April. By extrapolation of these data, a value of 1.4 Ci/g was obtained as the specific activity at 7:00 a.m. on 1 March. The estimation of radiation dose, especially that from internally deposited radioactive materials was difficult.

However, radiation from body surface was large enough to cause skin lesions. External radiation dose was estimated as shown in Table 1. The exposure dose for 14 days ranged from about 170 to 690 R, and nearly 60 per cent of these doses was received on the first day. This estimation was based on the results of the experimental reproduction of ash-fall, extrapolation of decay curves of many places of the boat, and on detailed investigation of

Table 1 Estimated dose of whole body gamma radiation.

Subject No.	First Day	Total
T-1	240~290 R	450~500 R
T-2	210~260	390~440
T-3	150~200	260~310* (360~410)
T-5	400~430	660~690
T-6	130~180	200~250
T-7	140~190	220~270
T-8	310~360	520~570
K-1	190~220	310~340
K-2	130~180	200~250
K-3	140~190	230~280
K-4	120~170	190~240
K-5	140~190	220~270
K-6	180~230	300~350
K-7	230~280	340~390
K-8	220~270	380~430
K-9	310~360	550~600
K-10	140~190	230~280
K-11	120~170	170~220
K-12	100~150	170~220
K-13	250~300	370~420
K-14	420~500	510~590
K-15	140~190	210~260
K-16	120~170	190~240

* T-3 put the fall-out material close to his bed. Therefore about 100 R should be added in total.

each patient's behavior on the boat. The dose to each person differed depending on his behavior and the position of his cabin.

The integrated dose to the thyroid from ^{131}I was inferred as about 20 to 120 rads from external countings of radioactivity in the thyroid region during the 4 to 7 weeks after the initial exposure.

Significant amounts of radioactivity were found in the urine samples collected at about 4 weeks after the explosion. The radioactivity decreased rapidly, namely at about 6 months post explosion the activity in the urine was barely detectable.

Radiochemical analysis of several organs from the fatal case showed that the radioactivity of these organs was clearly higher, when compared with the controls, although it was not extremely high (KIMURA et al., 1956).

After $8^1/_2$ years and 10 years, ^{137}Cs- and ^{90}Sr content in the urine of the fishermen revealed no significant increase. At the same time the results of whole body counting showed no significant difference between fishermen and controls.

Thus, the external irradiation seemed to play an impotant role in early effects.

SYMPTOMS AND SIGNS IN THE EARLY STAGE

Figure 1 summarizes the symptoms and signs in the early stage.

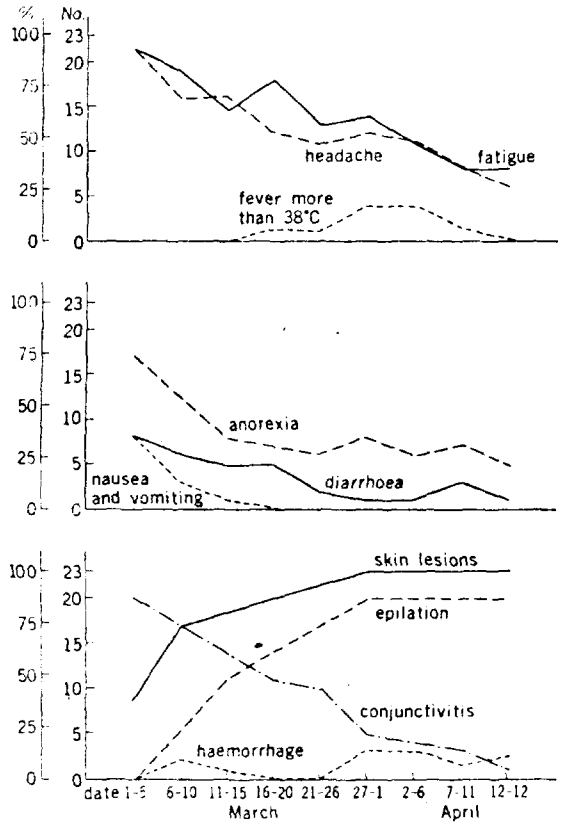

Fig. 1 *Symptons and signs in the early stage.*

HEMAT

1. **Leukocytes**

The total number of counts at about the 4th to count of less than 2,000 n one case, the leukocyte le between these minimum c Similar relationship was the dose as shown in Fig

Fig. 2 Correlation betwe the estimated doses to the wh body and the minimal num of neutrophils.

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3. **Platelets, etc.**

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HEMATOLOGICAL OBSERVATIONS

1. Leukocytes

The total number of leukocytes decreased gradually, showing minimum counts at about the 4th to 8th week after the exposure. Five cases revealed a count of less than 2,000/mm³, 13 less than 3,000, and 5 less than 4,000. In one case, the leukocyte level was depressed to 800. A correlation was found between these minimum counts and the doses of individual external irradiation. Similar relationship was found between minimum counts of neutrophils and the dose as shown in Figure 2.

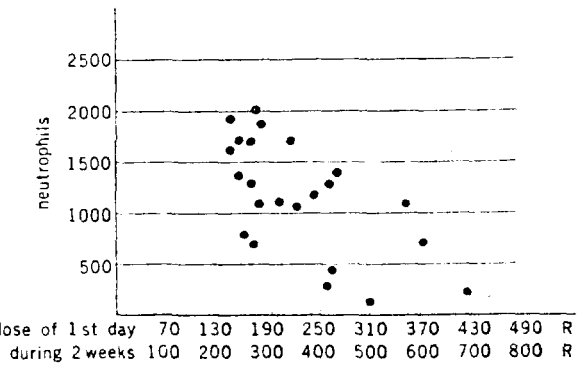

Fig. 2 Correlation between the estimated doses to the whole body and the minimal number of neutrophils.

In most cases a shift to the left of the neutrophils was observed. Staff cells increased in early stage and then gradually decreased. However, in some cases, metamyelocytes and myelocytes appeared in peripheral blood especially with the begin of recovery. In a fatal case who died of liver damage, a considerable number of juvenile neutrophils were observed at the end stage. Lymphopenia was noted between the 2nd and 8th week in all cases. Leukocyte count began to increase after the 8th week. In many cases eosinophilia was remarkable, especially with the indication of recovery. Eosinophilia continued in some cases for several years without proof of parasites, and one case still revealed slight eosinophilia in the 1968 survey.

2. Erythrocytes

At the time of hospitalization a few patients were anemic. No reticulocyte was observed in them at the critical stage. Color index was higher than 1.0. The Price-Jones curves of erythrocyte diameter were displaced to the right of normal at first, and returned to almost normal after one year. These changes corrseponded to changes of erythroblast diameters in bone marrow.

3. Platelets, etc.

Platelet counts decreased, reaching a minimum in the 4th to 7th week. Most of the fishermen revealed the values below 100,000/mm³. The results of other tests related to hemorrhage showed depression at the critical stage in general and recovered by the 10th week.

4. Comparison with Other Irradiated Cases

When these blood changes are compared with the changes of other irradiated

subjects, *i. e.* Hiroshima cases, Marshallese, and cases exposed by reactor accidents (HEMPELMAN et al., 1952 ; AMANO, 1953 ; CRONKITE et al., 1956 ; HASTERLIK and MARINELLI, 1956 ; GUSKOVA and BAISOCOLOV, 1956 ; ANDREWS et al., 1961 ; JAMMET, 1961), it is noted that all these cases similarly revealed the minimal value at about one month after exposure.

5. Bone Marrow

The bone marrow was aplastic at the critical stage in severe cases, which showed remaining and proliferation of plasma cells and reticulum cells. Figure 3 shows the bone marrow of one of the severe cases. Comparing with normal

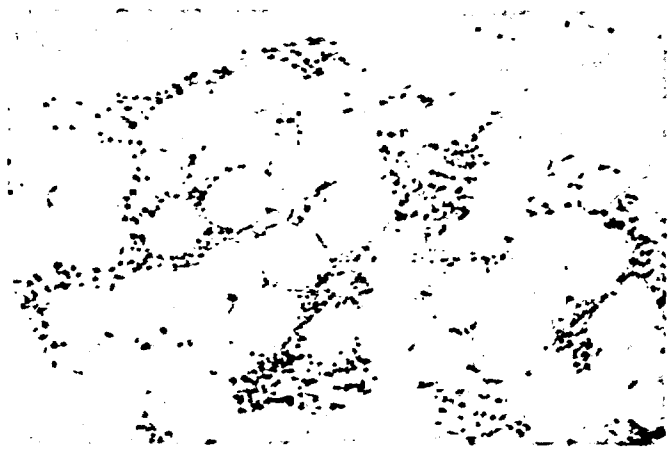

Fig. 3 Bone marrow of one of severe cases at 5th week.

bone marrow a lack of bone marrow cells was observed. With the beginning of recovery, aplastic marrow changed to hypoplastic and then turned into a type of maturation arrest. In some cases, recovery was not complete even after one year. In less severe cases, the bone marrow was not aplastic but hypoplastic or in a type of maturation arrest even at the critical stage.

6. Morphological and Functional Changes

Several morphological abnormalities were observed : nuclear debris of lymphocytes, binucleated lymphocytes, vacuoles of neutrophils, toxic granulations of neutrophils, degenerative changes of blood cells, mitotic abnormalities of erythroblasts, etc.

Motility and phagocytosis of neutrophils decreased remarkably. After one year, in some cases these functions were still lower than in normal persons.

FOLLOW-UP STUDIES

As above mentioned 16 to 18 fishermen have been examined on an annual basis.

Figure 4 shows the changes of the cumulative distribution curves of leukocytes. The curve of critical stage appeared displaced far to the left of the normal curve, and gradually approached normal values.

However, the curve of the 6th year was still displaced slightly to the left

Fig. 4 Leukocytes of Biki (J) (cumulative).

Fig. 5 Changes in t cytes, neutrophils ar

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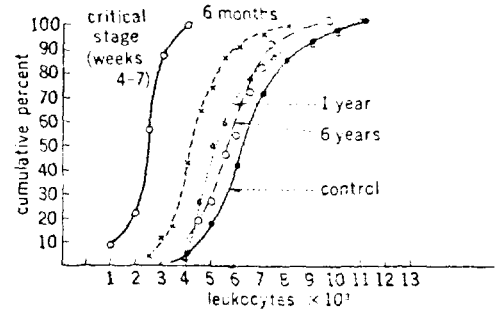

Fig. 4 Leukocytes of Bikini patients (J) (cumulative).

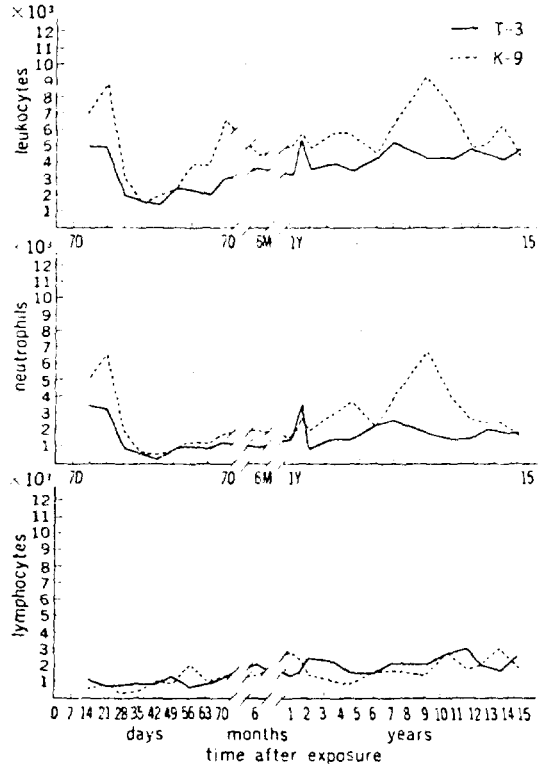

Fig. 5 Changes in the number of leukocytes, neutrophils and lymphocytes.

of normal Japanese. In the case of erythrocytes, 2 years after the exposure, the curve approximately came back to normal. A similar tendency is seen in the cumulative distribution curves of platelets.

However, in a few cases slight neutropenia is still observed. Figure 5 shows the changes of total leukocytes, neutrophils, and lymphocytes of 2 cases which are representative for severe injury.

A small increase of "mitotically connected abnormalities", *i. e.* karyomeres of erythroblasts, were observed in bone marrow smears of a few cases after 10 years.

Cytogenetical studies have been performed since several years. The results are summarized as follows (ISHIHARA and KUMATORI 1965 ; 1967 ; 1969).

1. The frequency of aneuploid cells was 2~3 per cent, which was not

Table 2 Chromosome abnormalities in peripheral lymphocytes of the fishermen, data from 1965 to 1967.

Cases	No. of cases examined	No. of cells analyzed	Aneuploid cells %	Stable cells % (/)*	unstable cells % (/)*
72-h culture:					
Control	10	693	2.88	0.14 (1/10)	0.14 (1/10)
Fishermen 1965	13	881	2.05	2.28 (9/13)	0.46 (3/13)
Fishermen 1966	15	1102	2.90	3.45 (14/15)	0.45 (5/15)
Fishermen 1967	16	1248	2.48	2.88 (15/16)	0.56 (6/16)
48-h culture:					
Fishermen 1966	10	750	2.27	1.20 (6/10)	0.67 (4/10)
Fishermen 1967	12	950	2.00	2.11 (9/12)	0.74 (6/12)

* Number of cases showing the abnormal cells per total number of cases examined.

so high (Table 2).

2. Unstable abnormalities such as dicentrics, etc. were observed (Table 2).

3. The frequency of stable abnormalities was remarkably higher than in controls (Table 2).

4. The detailed analysis of stable cells revealed that stable abnormalities were divided following 3 types:

a. stable cells with balanced chromosome constitution . . . 67 per cent

b. stable cells with deletion of a chromosome . . . 29 per cent

c. stable cells with excessive chromosome material . . . 4 per cent

5. In 3 cases small chromosomes which are similar to the Ph^1 chromosome were found.

6. The examined fishermen were classified in 3 groups according to the degree of the injuries indicated by the minimum values of neutrophils shown shortly after the exposure. It was found that the mean values of stable and of unstable cells were higher in proportion to the extent of the initial damage. Minimum values of neutrophils roughly corresponded to the estimated external radiation dose.

7. Chromosome abnormalities in bone marrow were observed in 5 cases. All of these abnormalities were limited to stable abnormalities. While stable cells in the peripheral lymphocytes showed various karyotypes of their own, these in the bone marrow were limited to only a few karyotypes.

SPERMATOGENESIS

As a generative tissue, spermatogenesis has many similarities with hematopoiesis. Therefore, the changes of number of spermatozoa is described for reference. The number of spermatozoa decreased, and minimum numbers were obtained in 16 cases about 8 months after the exposure. Lowering of mobility

and morphological abnormalities of spermatozoa were also observed. Indications of recovery were observed in some cases after about one year, but mostly first signs of regeneration did not show earlier than about 2 years after exposure, with following production of children.

SUMMARY

The hematological changes of Japanese fishermen exposed to fallout in 1954 were reported with other findings.

Generally speaking, it is difficult to estimate correctly the exposed radiation dose soon after the accident. Therefore, treatment of heavily irradiated persons should be decided by the daily appraisal of clinical and laboratory findings. From this point, hematological changes are an important information to decide the therapy which should be given to heavily irradiated subjects.

As to the Japanese fishermen, it seems to be very important as well as necessary to detect the significance of subtle changes such as they are still observed in hematological and cytogenetical examinations.

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DISCUSSION

Dr. CLIFTON (U. S. A.): Concerning the one fatality, would you care to comment on the nature of the liver damage, and its relationship to external or internal radiation exposure?

Dr. KUMATORI (Japan): Since this fatal case was anemic and revealed bone marrow aplasia, he received blood transfusions. Therefore, serum hepatitis can't be ignored. However, at the same time the existence of radiation-induced liver damage should be considered. At present it is difficult to decide the cause of his liver damage.

We should consider the probability of the radiation-induced liver damage, because in some publications we can see a similar histological picture of the liver of a patient who was irradiated therapeutically.

Dr. SANG (Korea): I thank you Dr. KUMATORI, I would like to ask you something about hemorrhagic tendencies on these cases. Would you tell me how long did hemorrhagic tendencies continue after the irradiation?

Dr. KUMATORI: In my cases the hemorrhagic tendencies were not so severe. The prolongation of the bleeding time was observed in a few cases. You can see normal bleeding time in most cases. In our cases, we used DUKE's method. The bleeding time is normally 3 minutes, and in 1 or 2 severe cases the bleeding time at the critical stage was as long as about 10 minutes. I think this came back to normal at about 10 weeks or so after the exposures, though I have no correct data here.

Dr. SANG: And how about the fibrinogen concentration?

Dr. KUMATORI: Fibrinogen concentration was almost normal from the beginning of the examination.

Dr. TUBIANA (France): I would like to ask Prof. KUMATORI if he has an idea of how uniform was the dose delivered to your fishermen. I ask you this question because we have a rather large experience of total-body irradiation for mostly kidney transplants in human patients, and there are 2 main differences between your results and the one we have also. The first one is that aplasia of the blood occurs much earlier in our patients, and the rigidity also occurs much earlier. The 2nd one is that the minimum number of leukocytes is much smaller in our cases, being of the order 1 to 200 leukocytes per cubic millimeter, after a dose of the

order of 350 R to 400 R (TUBIANA, M. and LALANNE, C. M., Annales de Radiologie, 6, 561, (1963) and in Effects of Ionizing Radiation on the haematopoietic tissue, Int. At. En. Ag., Vienna (1967)).

We have compared our curves with the curves of Yugoslavian accident cases, and here again we found the same difference, and our interpretation of these data was that probably the difference between the irradiated cases and the purposely irradiated patients was that in the irradiated patients the dose was very uniform, with a maximum variation of plus or minus 4 per cent, whereas in the case of accidents the uniformity was much less, and of the order of 30 per cent.

Dr. KUMATORI: I agree with your opinion. In my cases, I think, the main irradiation came from externally deposited sources--gamma irradiation. This is a type of uniform irradiation. And this irradiation played an important role in the hematological changes. The fallout material began to precipitate at 7:00 a. m. and continued to fall for about 5 hours. Therefore, the radiation dose to fishermen was at first small and then rapidly increased. As the fishermen began to clean up at about 12:00, the exposure rate decreased thereafter. They were irradiated continuously for 2 weeks with decreasing dose rates. Aside from this external irradiation, internal exposure may have had some effects. But the internal irradiation seemed to have only a slight effect on the acute hematological changes.