Effects of low dose irradiation on peripheral blood cell counts and their implication to health survey on radiological personnels

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末梢血球数に対する微量放射線の影響とその健康管理への応用

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微量放射線を受けている放射線取扱者の末梢血球数を色々の方法で調べた. Helde の方法に従つて血球数の累積百分率の形を調べると，微量を連続して受けていた取扱者と，事故のために一時可成りの量の被ばくを受けた者に変化が認められた．しかし，放射線取扱者の健康管理のためには血球数が一定の基準以下のものゝ百分率が被ばくの一つの目安によい．ただしこの方法は個人の健康診断に使うのは適当ではない．

I. Introduction

Changes in peripheral blood cell counts has been well recognized as one of the somatic effects of whole body irradiation. Thus the counts have been widely used as a criteria for radiation damage in health examination of radiological personnels. Especially at low doses it has been assumed that the reduction of leucocyte and/or erythrocyte counts is the only sign of radiation effect in many cases. In practice, hematological examinations have been carried out routinely in Japan in every radiological laboratory or factory with some dose control measures such as field survey and personnel monitoring of exposure. However, it is not generally agreed that definite hematological changes may be observed at very low doses near the former MPD range. As almost all radiological works are being carried out under as strict a control of exposure as possible according to the ICRP recommendations, some scientists have an opinion that the hematological control is of no value and ought to be dropped in favor of physical dose control.

In our previous report[1], hematological data on fifty to two hundreds radiological personnels obtained from 1954 to 1959 were presented. And the meaning of seasonal variations in blood cell counts was discussed. In the present paper former materials were re-examined with some recent data in addition from the standpoint th health survey of radiological personnels.

New methods to demonstrate the hematological effects of very low dose of radiation have been presented by Helde[2][3]. The evaluation and limitation of hematological control for radiological personnels including some methods proposed by him were mainly discussed.

II. Purpose of blood cell counts in physical examinations.

Hematological changes including peripheral blood cell counts are investigated as one of the measures for health examinations in radiological personnels. Thus, in order to evaluate the clinical significance of blood cell counts the purpose of the health examination should be both for personal and for group supervision, and their meaning may be different in these two cases:

I) As for personal health care, the detection of radiation damage in its early stage may be the first purpose of any examination. Furthermore, the results of the examination will be useful in determining whether there is any causual relationship between the disease and the previous irradiation, especially in case of leukemia.

2) As for health supervision of a group of radiological personnels the examination should be done in order to evaluate the condition of radiation control and working environment.

Radiological personnels should be always under strict control as to their radiation exposures. However, a routine regular health examination seems to be innevitable as a complemental mean to physical dosimetry to aim at perfection in health control of radiation personnel. The reasons are as follows:

A) It may be impossible to make area survey complete for space and time. Thus we can not relay all upon physical dosimetry for radiation control.

B) Personnel radiation monitoring generally done at present seems quite insufficient to determine the doses to various critical organs and tissues. It may give us only a guess of the exposure doses.

C) In an unexpected accident or in case of careless mistake of a personnel, physical measurement may often be missed. Blood cell counts may suggest some exposure in such a case.

D) It is generally assumed that leukemia may be induced with a low dose. As leukemia occurs after a long latent period, hematological data at irradiation may be very important for the presumption of the causual relationship between the irradiation and the disease.

E) Some biological phenomena such as changes in blood cell counts may be useful as a measure of biological dosimtries even if the phenomena may be only of physiological but not of pathological nature.

III. Characteristic features of blood cell counts

It is well known that personal difference and physiological fluctuation are generally observed in blood counts. And this is the reason for someone to insist upon disregarding the blood cell counts from health examination. However, in the present investigation blood cell counts were studied based on their characteristic features as follows:

1) Blood cell counts are quantitative features. Thus they themselves have no qualitative meaning for diagnosis.

2) Normal blood cell count show wide distribution in a population. Furthermore, physiological fluctuation seems to be rather large.

From these features, practical application of the examination should be limited as follows.

a) Only in a limited case, such as extreme count is observed, qualitative diagnostic meaning as for radiation damage may be given. This point will be discussed later.

b) Concerning a group of personnels, the form of frequency distribution, for example in the case of normal distribution not only means but also variances, will be used for analysis.

c) Concerning an individual personnel, the time course of the counts may give a clue for diagnosis in a special case in which a definite drift or an abnormal shift from the normal level is observed.

IV. Materials

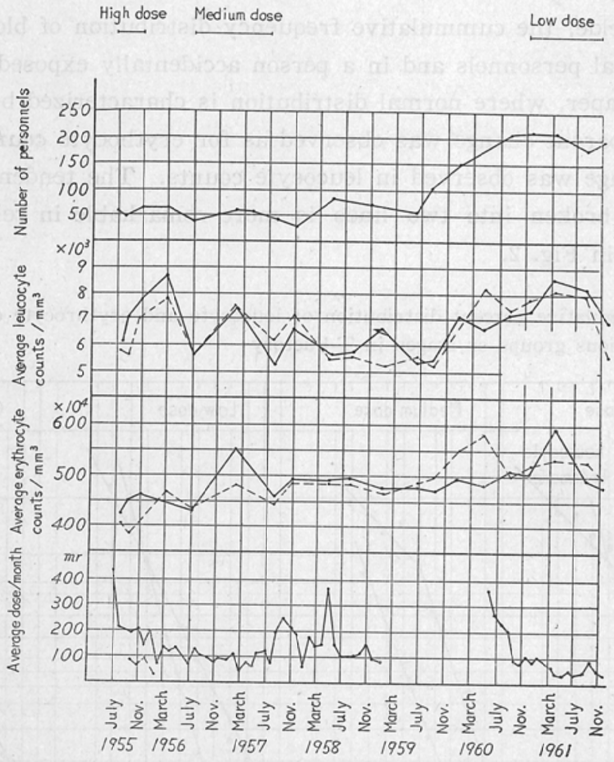
The results of health examination and personal monitoring in T-Factory since 1955 and those in O-Institute since 1959 were used as samples of various dose levels of irradiations.

In T-Factor X-ray and other radiation installations are being manufactured. There have always been workers in radiation buildings from fifty to two hundreds including both radiological personnels and other workers in the neighborhood of controlled area.

The results obtained so far are summarized in Fig. 1. Radiation dose before July, 1955 may be estimated to be more than 300 mr/w., as adequate means of radiation protection were not applied.

From 1956, the dose was reduced as shown in the figure to the level of 100 to

Fig. 1. Results of tho hematological and radiation control at T-Factory
—— Radiological personnel
...... Non-radiological personnel in the vicinity of controlled area



400 mr/4w., as average. Former MPD 300 mr/w was adopted in this period. In 1958 the systematic personal monitoring was not carried out because of the trouble arisen from the moving of the factory. In this period, the dose might be a little higher than before. However, since November 1960, as personal monitoring was started again with the new MPD 3r/13w, the dose has become lower and lower until it is at the level 50 mr/4w. as average. The materials are divided into three groups for high, medium and low level irradiation for convenience, though some of them include the same persons. Materials from July 1955 to November 1955 was assumed as a group of high dose irradia tion, those from July 1956 to July 1957 that of medium dose and those from November 1960 to November 1961 that of low dose. In addition blood cell count of nonradiological personnels far from the radiation building in the factory were done during the period from September 1960 to APril 1961 as a control.

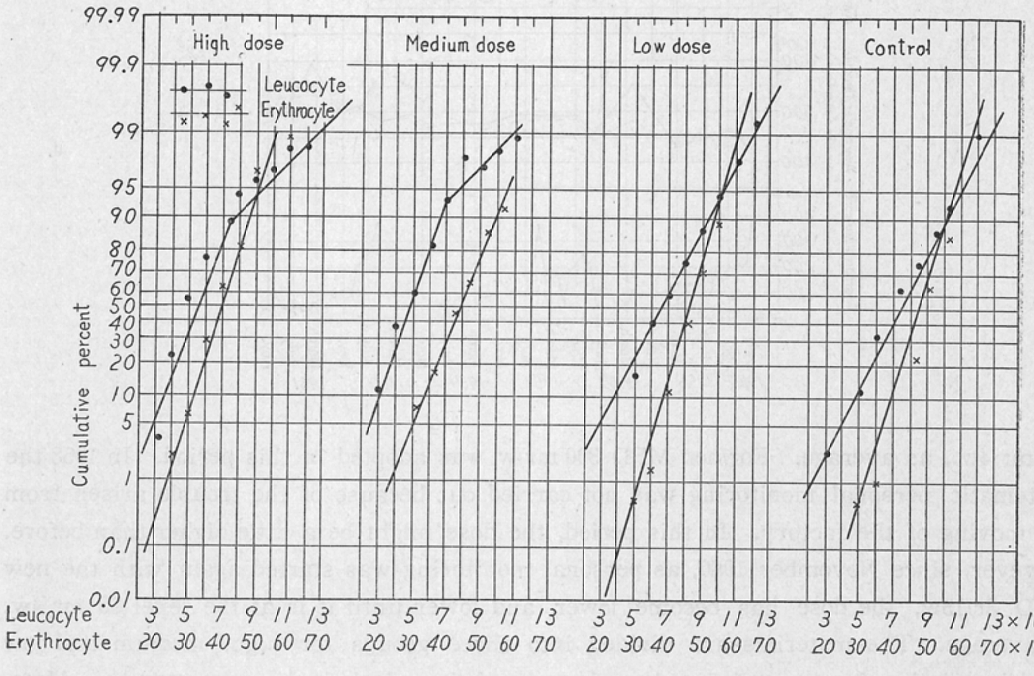
O-Institute is a research institute for the effects of radiations on polymers and their industrial applications. Various kinds of high energy apparatus have been installed.

The number of radiological personnels is about forty but some of them was alternated with others from time to time. Exposure dose is always below 20mr/2w. except an accidental case.

V. Form of frequency distribution

According to Helde, the cummulative frequency distribution of blood cell counts in a group of radiological personnels and in a person accidentally exposed were studied on normal probability paper, where normal distribution is characterized by a straight line. In T-Factory, no apparent change was observed as for erythocyte counts are concerned. But remarkable change was observed in leucocyte counts. The tendency for a normal straight line to be broken into two lines is more remarkable in relation to the dose irradiated as shown in Fig. 2.

Fig. 2. Cumulative percent distribution of leucocyte and erythrocyte counts in various groups or stages in T-Factory



In O-Institute, the distribution line become steeper according to the time course after the commencement of the radiological work as shown in Fig. 3. both for leucocyte and for erythrocyte.

But it is not sure that the disturbances are due to irradiation, as all workers started their work at the new institute, i.e, in a different environment than before. In the case of an accidental exposure, the slope of the line is apparently different before and after the accident (Fig. 4.).

In these cases, it may be generally accepted that when irradiated the line lies in the low number range with a steeper slope.

Fig. 3. Changes in cumulative percent distribution of leucocyte and erythrocyte counts during one year after beginning the radiological works in O-Institute

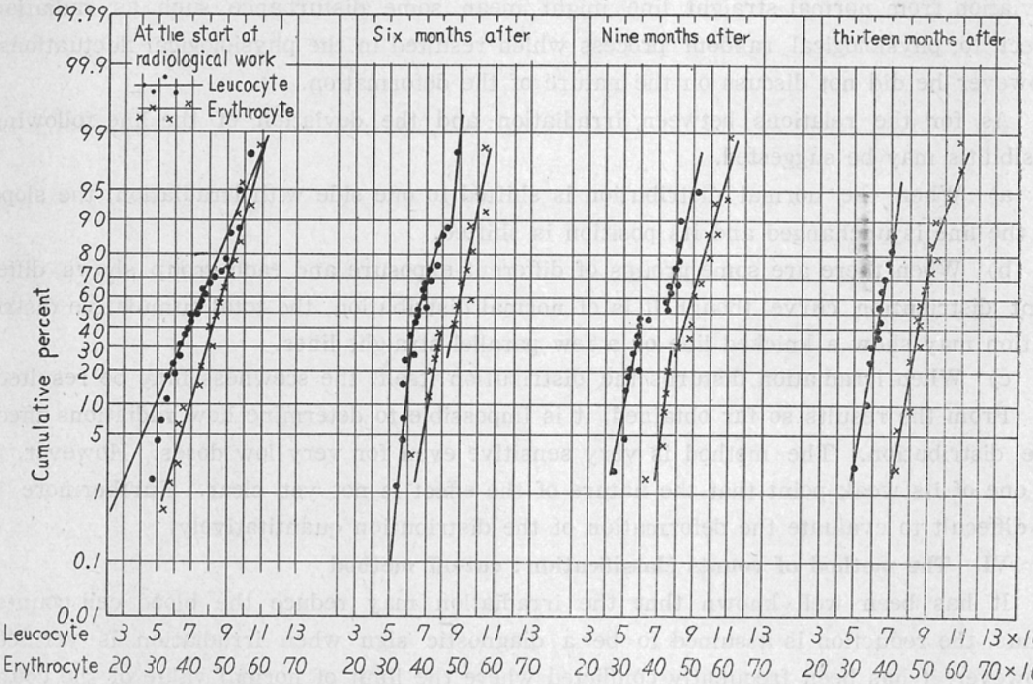
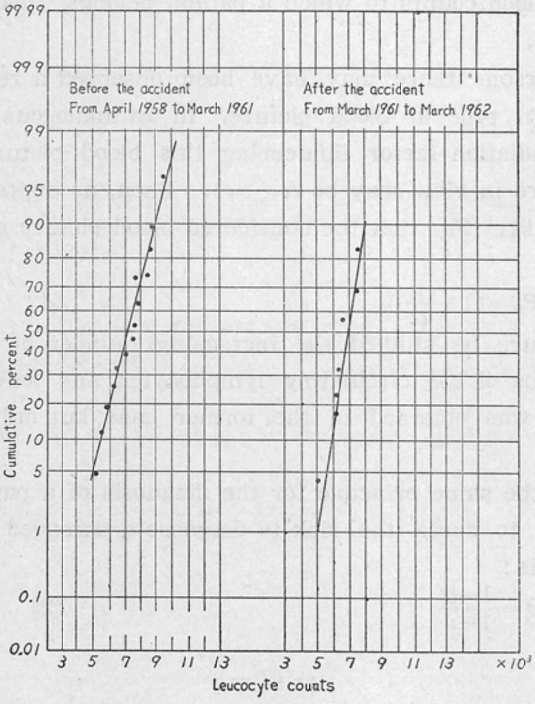


Fig. 4. Cumulative percent distribution of leucocyte counts in a personnel before and after an accidental partial exposure with high dose of electron beam.

* Estimated dose: electron beam (0.5 MeV) 1.5×10^4rad on his right hand 10r~100 mr on whole body



The results seem to be in accordance with those of Helde. He concluded that the deviation from normal straight line might mean some disturbance such as radiation effect to physiological random process which resulted in the physiological fluctuations. However he did not discuss on the nature of the deformation.

As for the relations between irradiation and the deviation of the line following posibilitis may be suggested.

a) When the normal distribution is shifted to one side with irradiation, the slope of the line is unchanged and its position is shifted.

b) When there are some groups of different exposure and each group shows different distribution curve though it is of normal distribution, the total cumulative distribution may show a knicked line or a few parallel straight lines.

c) When irradiation disturbs the distribution itself, the scewness may be resulted.

From the results so far obtained, it is impossible to determine how radiations affect the distribution. The method is very sensitive even for very low doses. However, it is one of its weak point that the nature of the effect is not yet clear. Furthermore it is diffecult to evaluate the deformation of the distribution quantitatively.

VI. The method of counts classification: cut-off method

It has been well known that the irradiation may reduce the blood cell counts. Thus, the reduction is assumed to be a diagnostic sign when irradiation is verified. However, it has been frequently conflicted where the limit of normal value of the count should be settled. In Japan, in the Report Form requested by the Ministry of Labor, the limits are temporarily settled as will be discussed later.

On the problem whether it is correct or not to diagnose radiation damage according to the range of the blood counts to which a patient belongs, Helde presented a clue to the solution as follows.

In a group of persons there may have been observed a relative frequency ν of persons with a certain type of blood picture. In an analogous group of persons but with an additional irradiation factor influencing this blood picture, the corresponding frequency of the picture in view may be α ($>\nu$). Then, as expression may be derived concerning the probability (P_{ir}) that the considered blood picture of the group is caused by radiation:

$$P_{ir}=(1-\frac{\nu}{\alpha}) \qquad (1)$$

As the blood picture he studied the increasing number of refractive neutral red bodies in the cytoplasma of the circulating lymphocytes and leucopenia. Avery high degree of probability was obtained in the former case but only fifty percent of probability in the latter.

In order to apply the same principle for the diagnosis of a patient in the irradiated group it is necessary to check the risk to diagnose a damaged as normal. The probability of the risk Q is:

$$Q=\frac{1-\alpha}{1-\nu} \qquad (2)$$

For the diagnosis of radiation sickness, following condition should be fulfilled at the 5% level as usually applied:

$$P>0.95 \text{ and } Q<0.05 \quad (3)$$

Table 1 shows P and Q values for some hypothetical cases of ν and α. From the table it may be concluded that only in extreme cases the condition (3) can be attained. Next, the question whether diagnostic accuracy can be improved or not by taking

Table 1. P and Q calculated on various values of ν and α

ν	α	P	Q
0.1	0.5	0.80	0.55
0.005	0.5	0.90	0.52
0.005	0.5	0.95	0.51
0.1	0.8	0.88	0.22
0.05	0.8	0.94	0.21
0.025	0.8	0.97	0.20
0.1	0.9	0.87	0.11
0.05	0.9	0.95	0.06
0.025	0.9	0.97	0.03

two or more types of blood picture independent to each other will be studied. For the second type, μ and β will be defined just as ν and α in the first type. The probability P' that the blood picture characterized by two criteria is caused by radiation:

$$P'=(1-\frac{\nu}{\alpha}.\frac{\mu}{\beta})$$

In order to P'> 0.95, only the product of $\frac{\nu}{\alpha}$ and $\frac{\mu}{\beta}$ should be less than 0.05 irrespective of the value of $\frac{\nu}{\alpha}$ or $\frac{\mu}{\beta}$. The condition seems less severe than that for one criterion for blood picture. However, the risk of faulse diagnosis taking the damaged as normal Q' is:

$$Q'=\frac{1-\alpha\beta}{1-\mu\nu}$$

It is far more diffecult to reduce the risk Q than to increase the probability of correct diagnosis P'. Thus the cut-off method is useful for group control but not proper for patient diagnosis in the case where quantitative features are in issue.

For group control, the proportion of personnels below the levels as for one or more criteria may be useful for the evaluation of the control.

Various limits for read-off method were applied to our data as trials. In the Report Form to the Ministry of Labor of Japan personels with the leucocyte count below 5,000/mm² are defined as abnormal and for erthrocyte counts below 4.5×10^6/mm².

The per cent proportions of personnels with abnormal blood count as difined sbove are shown in Table 3. In Table 3. 5,000, 4,000 or 3,000/mm² for leucocyte count and 4.5×10^4 for erythrocyte are taken as lower limits of normal counts temporarily.

Maximum P and minimum Q obtained in irradiated groups are shown in addition.

In Table 4,as the limit of normal counts the mean ±2 or 3 times the standard deviations in our control group are adopted. And the standard values reported by Hibino[4] are used similarly in the same table.

Table 2. Proportion of personnels with abnormal signs * according to Report Form to the Ministry of Labor, Japan (in per cent).

T-Factory:

Group or stage	Control	Low dose	Medium dose	High dose
Leucocyte	66.9	65.0	53.8	44.5
Erythrocyte	11.9	11.8	44.5	61.1

O-Institute :

Time of examination	1958			1959				1960
	April.	June	Oct.	Jan.	May.	Aug.	Nov.	Feb.
Leucocyte*	58.8	33.3	23.5	66.7	28.6	28.6	40.0	36.1
Erythrocyte	17.6	12.1	26.5	21.2	13.9	11.4	4.4	16.7

* As for leucocyte, the counts below 5,000/mm² or over 7,000/mm² assumed to be abnormal, and as for erythrocyte, those below 450 10^4/mm² in the Report Form.

Table 3. Proportion of level-off personnels in per cent and P-and Q-value according to arbitrary cut-off level in the case of personnels in T-Factory.

Group or stage		Control	Low dose	Medium dose	High dose	Max. P	Min. Q
Leucocyte Below	5,000	2.7	4.7	36.1	23.0	0.93	0.66
〃	4,000	0	0.3	10.9	3.2	1.00	0.89
〃	3,000	0	0	0	0	—	—
Erythrocyte Below	450×10^4	11.9	11.8	44.5	61.0	0.81	0.44
〃	400×10^4	1.0	1.9	16.8	29.4	0.97	0.71
Leucocyte below 5,000 and Erythrocyte below 450×10^4		0	0.8	25.0	9.2	1.00	0.74

From these tables the following may be discussed:

a) According to Report Form to the Mimistry of Labor, the P value obtained is too small for significance. As for leucocyte counts, contrary to expectation the number of personnels with abnormal counts seem to be reduced with irradiation. It may be incorrect.

b) The P value is significant when 4×10^6 red blood cells/mm² is adopted as the lower limit of normal value. However, the Q value is far from the significant one though it is the smallest among those so far tested.

c) If the breadth of 2 or 3 of normal distribution is adopted as the limit of normal counts, the relative frequencs of persons with abnormal counts in irradiated group is increased compared with non-irradiated control for erythrocytes but rather decreased for leucocyte.

The reason of this paradoxical results may be that the decrease of the mean exceeds the increase of the variance though both changes are due to irradiation.

Table 4. Proportion of level-off personnels in per cent and P-and Q-value according to such a cut-off level as mean $+2\sigma$ or $\pm 3\sigma$ for the control distribution of the standard distribution by Hibino.

Group or stage		Control	Low dose	Medium dose	High dose	Max. P	Min. Q
From our control distribution*							
Leucocyte	over mean $+2\sigma$	4.1	3.9	2.8	1.5	—	—
	below mean -2σ	2.9	3.5	29.4	16.2	0.90	0.62
	out of mean $\pm 2\sigma$	7.0	7.4	32.2	17.7	0.78	0.73
	overmean $+2\sigma$	1.7	0.9	0.9	0.8	—	—
	below mean -2σ	0	0	0	0	—	—
	out of mean $\pm 2\sigma$	1.7	0.9	0.9	0.8	—	—
Erythrocyte	over mean $+2\sigma$	2.3	2.1	2.8	0	—	—
	below mean -2σ	0.6	1.1	20.7	28.5	0.98	0.72
	out of mean $\pm 2\sigma$	2.9	3.2	23.5	28.5	0.90	0.74
	over mean $+3\sigma$	0	0.6	2.8	0	1.00	0.97
	below maen -3σ	0.6	0.3	1.8	9.2	0.93	0.91
	out of mean $\pm 3\sigma$	0.6	0.9	4.6	9.2	0.93	0.91
From Hibino's data**							
	over mean $+2\sigma$	25.0	20.8	4.5	3.8	—	—
	below mean -2σ	0	0.6	11.9	4.7	1.00	0.88
	out of mean $\pm 2\sigma$	25.0	21.4	16.4	8.5	—	—
	over mean $+3\sigma$	9.3	7.9	3.6	2.3	—	—
	below mean -3σ	0	0	0	0	—	—
	out of mean $\pm 3\sigma$	9.3	7.9	3.6	2.3	—	—
	over mean $+2\sigma$	11.6	9.5	5.5	0	—	—
	below mean -2σ	0.6	0.8	7.3	15.7	0.96	0.85
	out of mean $\pm 2\sigma$	12.2	10.3	12.8	15.7	—	—
	over mean $+3\sigma$	1.7	2.6	3.6	1.6	—	—
	belowmean -3σ	0	0	0	3.1	1.00	0.97
	out of mean $\pm 3\sigma$	1.7	2.6	3.6	4.7	0.64	0.97

Standard distribution	mean $\pm$ standard deviation
*Our control distribution	$8,100 \pm 1,670$ for leucocyte
	$522\times10^4 \pm 63\times10^4$ for erythrocyte
*Hibino's standard distribution	$6,600 \pm 1,300$ for leucocyte
	$476\times10^4 \pm 58\times10^4$ for erythrocyte

d) By means of combined use of two criteria for leucocytes and erythrocytes it was succeeded to obtain P=1. Even in this case the Q value is not sufficiently small.

VII. Conclusion

It may be concluded from the above examination that the method of cumulative frequency distribution of blood cell counts is a very sensitive measure for whole body irradiation if the existence of any other causes to modify the distribution can be denied. However, it must be emphasized that a slight disease or even menstruation in female may disturb the distribution. The quantitative evaluation of the deformation may be very difficult. In these points, the cut-off methods is better for the group control though it is quite risky to apply the method imprudently for personal health care at very low doses.

Concept of radiation damage in personnel health control may be confused at present. Temporary response to radiation may be assumed as physiological in some cases and as pathological in other cases. In order to achieve the purpose mentioned in Section II, the concept should be settle at first. The present study may present some clue on the problem.

Summary

Peripheral blood cell counts of radiological personnels exposed with very low dose of radiation were studied. By the method proposed by Helde, changes in the form of cummulative percentage distribution was observed in the irradiated group and in a person accidentally exposed with a relatively high dose.

But for the health survey of radiological personnels the percentage of personnels with the blood cell count below a certain limit may be prefered as a good measure for the exposure if an adequate limit is adopted, though the method is not appropriate for the personal health care.

Feferences

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