Studies on Radiation Disturbances
during Treatment of Uterine Cancer. Especially on the
Radiopathogenic Substance and New Therapy

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We often experiment the radiation disturbances (RD hereunder), that is
leucopenia, thrombocytopenia and sympathetic nervous syndrome, while admini-
stering radiotherapy following operation of uterine cancer and such malignant
neoplasms and against advanced malignant female genital tumors. They some-
times become so pronounced as to necessitate suspension of the therapy at
times even forcing us to waste the most precious time for inhibiting growth of
the neoplasm. The present authors have made some researches upon the patho-
genic factor that induces such RD, and a summary of the results obtained
hitherto is presented in the following.

I. EXPERIMENTS ON RD

1. On the Radiopathogenic Substance

1) Investigation on the existence of radiopathogenic substance

After rabbits were irradiated serially with X-ray to induce RD, blood was
sampled from them and analysed into 3 parts of blood cells, serum and plasma.
Upon injecting these blood parts separately in normal rabbits, it was found that
the blood cells had the strongest effect in inducing RD. The substance supposed
to give this effect of causing RD to blood cells will be called radiotoxin hereunder.

2) Extraction of radiotoxin

Blood cells sampled from the rabbits that showed the severest symptoms of
RD were subjected to dialysis, fractional extraction with alcohol, ether and so
forth, as shown in Table I, and radiotoxin was successfully isolated. This is a
low molecular substance but the chemical constitution and characteristics are
now under investigation.

3) Action mechanism of radiotoxin

Intravenous injection of radiotoxin induces pronounced decrease of leuco-
cytes, as shown in Fig. 1, but when it was injected with pregicil, an autonomic nerve blocker, the decrease of leucocytes was inhibited and when administered in mixture with pereston N, a conjugating detoxicant, the decrease of leucocytes was not inhibited, as shown in Fig. 2, but only the reincrease to normal level was accelerated. The decrease of leucocytes by radiotoxin, therefore, seems to be induced through the intermediary action of the hypothalamus, the seat of centers for adjustment of blood cells and of the autonomic nerves.

4) Confirmation of the radiotoxic effect

Blood cells sampled from rabbits receiving radiotoxin in serial injections, when separated from plasma and injected in normal rabbits, cause pronounced decrease of leucocytes. This result convinced us of the existence of some component in such blood cells responsible for the RD.

5) Histological changes in entrails following injection of radiotoxin

Following injection of radiotoxin, histological changes were chiefly observed in the detoxicating and excreting organs, the liver and the kidneys, only slight changes being found in the other organs.
Fig. 1. Experimental results of radiotoxin a injection (20~50 mg.). Total leucocyte count.

Fig. 2. Results of mixed injection of radiotoxin and Plegicil or Pereston N. Total leucocyte count.
Fig. 3. Survival rate of mice pretreated with tranquilizers. 50 mice per group. Irradiation: 500 γ.

Fig. 4. Survival rate of mice pretreated with tranquilizers. 50 mice per group. Irradiation: 500 γ.
2. Causes of Radiation Sickness and Decrease of Leucocytes and Platelets

A. Animal Experiments

1) RD and the autonomic nerve system

Various tranquilizers (autonomic nerve blockers) were administered in one dose each to mice one hour before X-ray irradiation, and it was found that the survival rate was obviously enhanced by such pretreatment, as shown in Figs. 3 & 4. Another experiment showed that the ChE activity in the hypothalamus, the seat of the autonomic nerve center, and its marginal systems is altered by X-ray irradiation, as shown in Fig. 5.

Fig. 5. Change in ChE concentration in the hypothalamus and the hippocampus following X-ray irradiation. Ordinate: ChE activity.

2) RD and the adrenocortical system

X-ray irradiation constitutes a stress for a living organisms, and, as many other non-specific stresses, probably induces a reaction chain of general adaptation syndrome in a body, causing activation of a series of endocrine defense processes through the agency of the hypophysis-adrenocortex system; acting upon such an assumption, we pretreated the experimental animals as above with adrenocortex-activating agents and found the survival rate enhanced, as shown in Fig. 6.
Fig. 6. Survival rate of mice treated with some drugs before or after irradiation. 25 mice per group. Irradiation: 500 R.

Fig. 7. Survival rate of mice treated with some drugs before or after irradiation. 25 mice per group. Irradiation: 500 R.
3) RD and detoxicating function

Experiments of administering drugs with conjugation-detoxicant, hepatotonic or hematopoietic agents were conducted with radiotoxinated mice, and again a rise of survival rate was affirmed, as shown in Fig. 7.

B. Clinical Tests

The following tests were performed to determine whether the above results of animal experiments are available for clinical purpose.

1) RD and the autonomic nerve system

The flicker values in the subjects showing symptoms of radiation troubles, as estimated with a Motokawa’s electric flicker-meter and reflecting the activity of autonomic nerves, were found more strongly affected than in the non-RD controls, as shown in Fig. 8; in the subjects administered up to about 30 rounds of 300 r each, the change in the flicker value was found to run parallel with the grade of radiation sickness and leucopenia, as shown in Figs. 9, 10, and 11.

2) RD and the adrenocortical system

The 17KS value rises transiently with irradiation, to reach the maximum after the 5th irradiation or so, then comes down approximately to the pre-irradiation level, begins to rise again in a wavy course after about the 25th round, to reach another peak at about the 30th round of irradiation, and dropped off rapidly thereafter. The 17OHCS value changed in a similar way but somewhat lagging behind the 17KS value. The change in flicker value also ran a

Fig. 8. Electric flicker values in cases with and without radiation disturbances during radiotherapy. Abscissa: Rounds of irradiation.
parallel course with that of 17KS to some extent. These finding suggest that exposure to radiation, besides stimulating the autonomic nerve system, acts as a stress upon the adrenal glands, to stimulate their secretion of 17KS and 17 OHCS. Both the 17KS and the 17 OHCS values were higher in the radiation
disturbances than in the non-radiation disturbances controls (Figs. 12 and 13), and the fluctuation in 17KS value ran nearly parallel to the grade of radiation sickness, but was not related with the leucopenia.

Fig. 11. Occurrence of leucopenia and thrombocytopenia.

Fig. 12. Relationship between radiation disturbances and 17KS content in urine.
3) RD and the enzyme systems

a. Catalase system: The catalase activity of blood cells and serum as estimated with a Stern and Battelli’s apparatus, apparently fell off slightly with repeated irradiation, but the trend showed no significant correlation with the presence or grade of RD.

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Fig. 13. Relationship between radiation disturbances and 17 OHCS content in urine.

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Fig. 14. ChE concentration in cases with radiation sickness and leucopenia. Ordinate: ChE activity.
b. ChE system: There is as yet no incontrovertible theory on the correlation between the autonomic nerve function and ChE. On the other hand, there is an undeniable close correlation between serum ChE and the hepatic function. We found the ChE activity of blood cells and serum, as determined by Kasuga's method\(^5\), was lowered by irradiation, especially when the irradiation was repeated beyond 30 rounds; the serum ChE value fell in parallel with the fall in flicker value in the subjects with radiation sickness or leucopenia (Fig. 14.), but the parallelism went as far as the 30th round of irradiation and no farther. The strong drop of the serum ChE activity beyond the 30th round of irradiation is probably due to the impairment of hepatic function by radiotoxin.

C. Cause of Radiation Anemia

The porphobilinogen, coproporphyrin and protoporphyrin contents in urine were found increased when the irradiation was repeated beyond 30 rounds and especially largely in the cases prone to anemia. It seems that radiation anemia is induced by the effect of large doses of irradiation acting inhibitorily on the porphyrin metabolism in the hematopoietic organs.

II. TREATMENT OF RD

1. Treatment of Radiation Sickness

Considering the frequency of radiation sickness attributable to anomaly of the autonomic nerve system, the cases were first treated with tranquilizers (perphenazine, prochlorperazine, acetylpromazine, meclizine hydrochloride, etc.) one hour before irradiation, and satisfactory results could be attained. PVP preparations, essential amino-acid preparations, pantothenic acid, $\varepsilon$-amino caproic acid and thioctic acid were also used.

2. Treatment of Leucopenia

The transient decrease of leucocytes at the beginning of radiotherapy seems to be due to an anomaly in the blood-cell adjustment center by radiotoxin but the leucopenia following repeated irradiation seems to be attributable to a derangement in the hematopoietic organs caused by radiotoxin. Accordingly, we make it a rule to test the hematopoietic function by cobalt-greenpole method\(^6\) and adenine method\(^7\), to assure choice of best-adapted medicine. As adrenocortical hormones cortisone, predonisolone, methylpredonisolone, and dexamethasone were used. The nonhormonous drugs (cobalt-greenpole, adenine, orotic acid, aminoacids, cystine and PVL) were also employed for treatment.

3. Treatment of Thrombocytopenia

Sometimes thrombocytopenic purpura is experienced during radiotherapy, so that a decrease of blood platelets should not be made light of. For fighting
this anomaly, adrenocortical hormones are prominently efficacious; no sure efficacy can be expected from any other drug.

4. Treatment with X-rayed Blood

At this clinic, the following treatment is given to cases with leucopenia or thrombocytopenia; 100 cc of fresh blood is sampled with a syringe containing 10 cc of 10% citric acid solution, exposed to X-ray irradiation under the conditions of; generator, Toshiba KXC-18 ; tube voltage, 180kv ; tube amperage, 20 mA ; filter, Cu 0.7 + Al 0.5 ; distance, 40 cm ; irradiation rate, 66.7 r/min ; irradiation dose, 300 r, and is then injected in the same manner as in blood transfusion. This treatment has proved notably effective in 40.9% and 40.5%, and less notably effective in 36.4% and 48.7% of leucopenia and thrombocytopenia cases, respectively. In some cases, the treatment was successful even when adrenocortical hormone treatment failed.

For further details on the theory and practice of the above treatments against RD, the readers are referred to our original report31 in Journal of the Japanese Obstetrical and Gynecological Society.

III. CONCLUSION

The results of our experiments summarized in the above seem to lead to the following conclusions:

Radiation disturbances are probably caused by production in the irradiated body of a substance that may be called radiotoxin, which induces first radiation sickness and leucopenia through the agency of autonomic nervous center, while the stress due to the irradiation deranges the function of endocrine organs through the agency of hypophysis-adrenocortex system. A persistent course of radiotherapy causes by itself and through the agency of radiotoxin it produces a hypofunction of the hematopoietic organs, the liver and the kidneys and thus lead to occurrence of radiopathic symptoms of anemia, etc.

Accordingly, for treating cases of such radiation disturbances, measures should be taken first to assure relief of disturbance in the autonomic nerve center and at the same time to relieve the patient from radiation stress, for fighting the radiation sickness in the early stage, and attention should be directed to the recovery of normal function of the affected organs in the more advanced stages.

References

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