CLINICAL-HEMATOLOGICAL, BIOCHEMICAL, AND MORPHOLOGICAL CHANGES DURING CONVALESCENCE IN THE THERAPY OF RADIATION SICKNESS

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The complex methods now widely employed for treating radiation sickness are usually based on intravenous or subcutaneous injection of drugs [4, 5]. We attempted to treat acute experimental radiation sickness with preparations whose therapeutic action we had previously studied [1, 2, 3, 6, 7], administering them solely per os.

EXPERIMENTAL METHOD

The experiments were conducted on 29 dogs weighing 9-16 kg (14 experimental and 15 control animals), which were subjected to whole-body x-irradiation in a dose of 600 R on a two-tube RUM-3 apparatus (voltage—200 kV, current—15 mA filters—0.5 mm Cu and 1 mm Al, skin-focus distance—100 cm). Under our conditions the LD 80/30 was 600 R; this dose causing severe or moderate acute radiation sickness.

All the experimental animals received batyl alcohol (batylol) and leucogen in 0.02 g tablets immediately after irradiation and were also given one tablet of kaferide after 6-7 days. The dogs simultaneously received 100,000 units of biomycin daily for the first 10 days and 0.25 g of levomycetin daily for the next 10 days. They received all the drugs twice daily.

The batyl alcohol was given for one month and the leucogen and kaferide for 2-2.5 months. If their hematological indices had not returned to normal within 3-4 months after irradiation the animals were again given batyl alcohol and kaferide for 2-4 weeks.

EXPERIMENTAL RESULTS

Twelve of the 15 control (untreated) dogs died 9-22 days after irradiation. They developed severe acute radiation sickness. Severe leucopenia was observed during the first few days after irradiation and at the height of the illness, i.e., from the 8th to the 12th day, the leucocyte count was 400-500 per mm^3 and 150 per mm^3 in certain cases These dogs simultaneously developed severe thrombopenia, reticulopenia, and marrow aplasia. On dissection, the dead dogs exhibited the typical pattern of severe acute radiation sickness, with marked symptoms of hemorrhagic diathesis and atrophy of the follicular apparatus in the lymph nodes, spleen, and alimentary tract accompanied by infectious complications. The illness took a milder form in the three animals which survived. The leucocyte count of dog No. 25 (Fig. 1) was 400-600 per mm^3 on the 22nd-26th day and 900 per mm^3 on the 33rd day; thrombocytes were detected in the form of single cells and the bone marrow was destroyed.

Two of the 14 treated dogs died (on the 9th and 26th days). The symptoms of radiation sickness were slight in the dogs which survived: there was no hemorrhagic syndrome, dyspepsia, or loss of weight. Only a few animals exhibited a brief loss of appetite and shedding.

The changes in hematological indices were slight (Fig. 2). The developing marrow hypoplasia did not pass into aplasia in a single case: intensive erythroblastic hyperplasia was observed. The bone marrow returned to normal

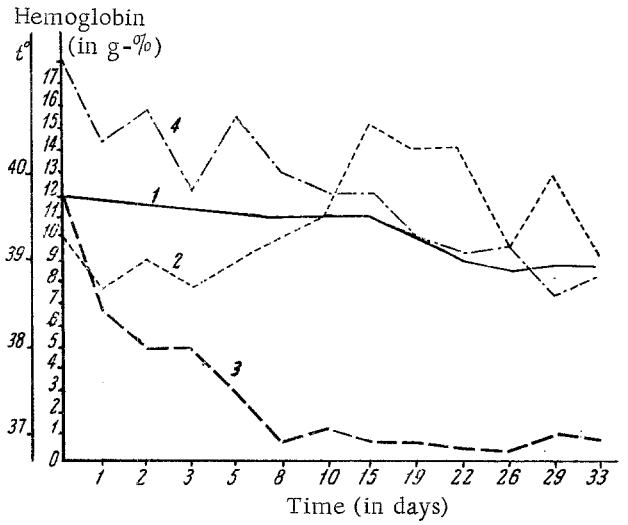

Fig. 1. Changes in weight (1), temperature (2), leucocyte count (3), and hemoglobin count (4) in control dog No. 25. 5) Hemoglobin (in g-%); 6) time (in days).

no sooner than 2-3 months after irradiation. At this time the erythrocyte and hemoglobin counts somewhat exceeded their initial levels. The maximum leucopenia (900-1300 leucocytes per mm^3) was recorded in the treated dogs 7-22 days after irradiation. In the majority of cases the leucocyte count did not drop below 2000 or even 3700-4000 per mm^3. Normalization of the leucocyte count began on the 13-24th day. A slight anemia was observed in certain dogs (Nos. 35, 36, and 42) at later times. In only one dog (No. 30) did the erythrocyte count drop to 1,810,100 and the hemoglobin content to 4.6 g-%. The erythrocyte count ordinarily did not go below 4,000,000-5,000,000, while the hemoglobin content remained above 9-10 g-%. The reticulocytes did not disappear in all the dogs; when this did occur they reappeared after 5-20 days. Prolonged thrombopenia was observed in all the animals and the thrombocyte count reached normal levels by the end of the experiment (after 6 months) in only a few of the dogs.

The mild radiation-sickness course and the restoration of the functioning of the hematogenic organs in the treated dogs were confirmed by the data obtained in pathomorphological investigations. On dissection of 8 dogs which were treated and then killed 2-4 months after irradiation symptoms of hemorrhagic diathesis and changes caused by infectious complications were not detected in a single case. Histological examination of the spleen showed that it retained a sufficient number of follicles. No destruction or atrophy of the follicular apparatus was observed in the lymph nodes and the follicular structures located along the alimentary tract. To the contrary, the follicles and myeloid strands were intact and this to some extent indicated a restoration and normalization of lymphopoiesis. An iron-containing pigment was frequently detected in the cells of the reticuloendothelial system; this indicates an improvement in the phagocytic and enzymatic capacity of its cells. Vasodilation was noted in the lungs, liver, and kidneys. At the same time, dystrophic changes were observed in the muscles, liver, and kidneys, but they were considerably less marked than those in the control animals. Complete remission of these changes apparently requires a longer time.

A decrease in the peroxidase activity of the blood was characteristic of the recovery period for both the control and experimental dogs, setting in during the height of the illness and increasing in extent with the severity of the animal's condition.

During the recovery period the total phosphorus content was normalized in the treated animals 20 days after irradiation and, in certain cases, had a tendency to increase slowly. Conversely, the total phosphorus content in the blood of the control dogs increased until the 33rd day, reaching a twice-normal level in 2 of the 3 animals.

The most characteristic changes occurred in the creatine and creatinine content. After a more or less marked increase or decrease during the height of the radiation sickness the creatine content of the blood of the treated dogs decreased in an irregular fashion during the recovery period, being subnormal by a factor of 1.5-2 in certain animals; conversely, in the control animals it increased in parallel with the total phosphorus content and exceeded the normal level by a factor of 1.5 by the 33rd day.

The serum content of readily separable iron varied considerably less in the treated dogs than in the control animals; in both cases the acute radiation sickness was induced by massive whole-body irradiation. The serum content of readily separable iron increased steadily from the 10th-15th day onward in the dogs which received drugs and reached or even exceeded its normal level by the 30th day. In contrast, in the control dogs, the serum content of readily separable iron dropped sharply immediately after irradiation and, after a brief rise on the 3rd-5th day, apparently caused by intensified erythrocyte hemolysis, continued to decrease until the animal died (on the 9th-20th day). From the 25th-30th day after irradiation onward the surviving control dogs exhibited a slow irregular rise in readily separable iron content.

Tissue respiration and reserve alkalinity were investigated in special series of experiments on rabbits and rats.

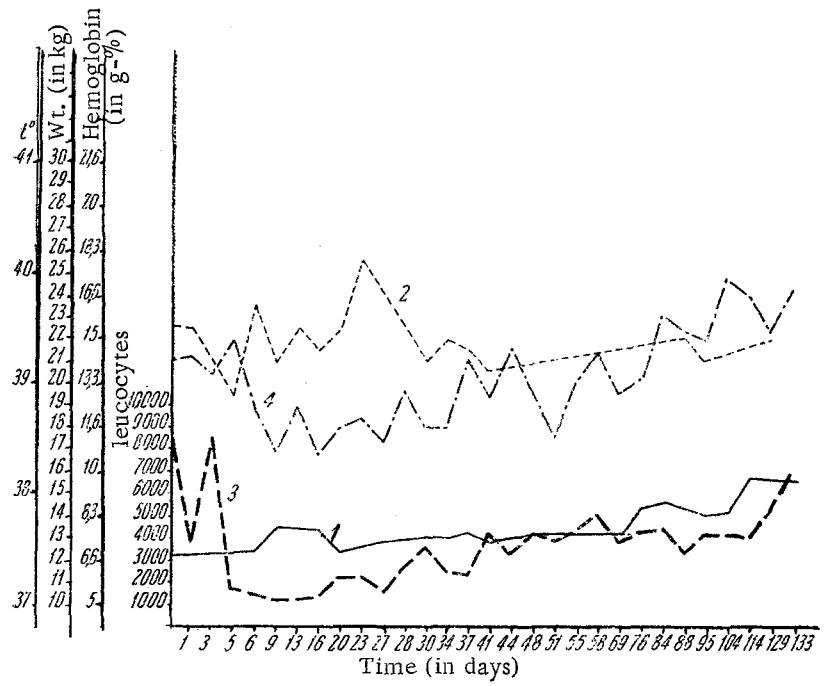

Fig. 2. Changes in weight (1), temperature (2), leucocyte count (3), and hemoglobin count (4) in dog No. 31, which was treated after irradiation in a dose of 600 R. 5) Weight (in kg); 6) hemoglobin (in g-%); 7) leucocytes; 8) time (in days).

Tissue respiration and reserve alkalinity remained within normal limits in the rats which were given drugs after irradiation (see table). The rabbits which received batyl alcohol after irradiation exhibited a cerebral and, especially, myocardial tissue respiration more intensive than that of the control animals.

Leucocyte Count, Reserve Alkalinity, and Oxygen Absorption of Skeletal Muscle in a Rat Two Months after Irradiation and Influence of Batyl Alcohol, Leucogen, and Kaferide on these Indices

Experimental conditions	Leucocyte count, per mm^3	Reserve alkalinity (in %) by volume CO_2)	Oxygen absorption per 100 mg of tissue during 2 h of respiration
Irradiation, 800 R	2650 1200-3600	41.3 39.0-42.8	21.48 12.70-33.50
Irradiation, 800 R + batyl alcohol, leucogen, and kaferide	10580 9000-11500	48.5 46.2-50.0	43.99 36.9-47.38
Control (no irradiation)	11700 9500-17200	48.2 36.0-62.4	44.93 38.61-55.28

All the treated dogs exhibited a considerably smaller (by an average of 30-40%) and less prolonged decrease in blood-flow rate than the control animals, in which it reached 20-25 sec as compared with 10-14 sec before irradiation. The complex of drugs employed thus increased the survival rate among the irradiated animals and promoted a milder radiation sickness. Tests of leucogen, kaferide, and batyl alcohol on unirradiated animals showed that these drugs not only stimulate leucopoiesis, but also affect the phosphorus, creatine, and readily separable iron contents, reserve alkalinity, and tissue respiration, i.e., indices closely associated with the basic metabolic processes disrupted by ionizing radiation.

We feel it necessary to note that batyl alcohol, which is not a component of any of the known biologically active substances (hormones, enzymes, or vitamins), is present in the bone marrow (the nonsaponifiable fraction of the

white marrow) and in the liver. Abroad it has been obtained from shark livers and is prescribed in leucopenia and anemia [11-19]. In the Soviet Union it has been synthesized by Prof. M. N. Shchukina (Scientific Research Institute of Chemistry and Pharmacy). One constituent of kaferide is calendulin, which is used as an antiseptic for treating inflammations and promoting the healing of wounds [8, 9, 10].

In conclusion we may advance the hypothesis that the successful therapeutic action of the preparations which we employed in treating radiation sickness must be attributed to a considerable extent to their influence on the organism as a whole, rather than to their effect on the individual processes disrupted by ionizing radiation.

SUMMARY

Immediately after the general irradiation with 600 R the dogs were given butyl alcohol and leucogen in a dose of 0.02 g, in 6-7 days kaferide was added in a dose of 0.2 g. Simultaneously for the first 10 days these dogs received biomycin in a dose of 100,000 units and the next 10 days—levomycetin in a dose of 0.25 g. All the preparations were administered per os, twice a day: butyl alcohol was given for 1 month, leucogen and kaferide—for 2-2.5 months. Of the 14 dogs treated 2 died on the 12th-26th day; of the 15 control animals—12 died on the 9th-22nd day. In the surviving animals radiation sickness was comparatively mild without any marked changes in behavior, temperature, weight and hemopoiesis; marked, but not prolonged leucopenia (900-1,300 per cubic mm) was observed only in several dogs in the absence of complete bone marrow depletion present in the majority of control dogs. Postmorten and histopathological examination of the organs and tissues of the treated dogs performed 2-4 months after irradiation also confirmed the mild course of radiation sickness. There were no marked changes in the biochemical blood indices characteristic of acute radiation sickness (peroxide activity, total phosphorus, creatine, readily splitting iron).

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