

Effects of X-Rays and Nitrogen Mustard on Lymphatic Nodule of the Rabbit.* (17554)

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The relationships between the dose and the histologic effects of total body radiation with X-rays on the lymphatic nodule has been reported previously.(1) It was found that the sequence of histologic changes in the lymphatic nodules is characteristic for different dose levels. Total body radiation of rabbits with 800r and 600r at a rate of 16r per minute produces a rapid and complete destruction of the lymphatic nodule resulting in a nodule-free period beginning at 5 days with a subsequent regeneration at 21 days after radiation. Lower doses (400r and lower) produce only a partial destruction of the lymphatic nodule with an immediate regeneration so that no nodule-free period occurs. For a detailed description of the changes in the lymphatic nodule after X-rays, we refer to previous papers.(1) The similarity between the hematotoxic effect of X-rays with that of nitrogen mustard is well known and has been reported by a number of investigators. It seemed to us of interest to investigate whether this similarity extends itself to the histologic effects on the lymphatic nodule and if so, to compare, on this basis, the degree of the effect on the lymphopoietic system of these two agents with respect to their general toxicity to the organism. The nitrogen mustard compound used for this investigation is methyl bis (B-chloroethyl) amine hydrochloride.

The LD₅₀ dose is taken as a measure of the general toxicity of X-rays and nitrogen mustard. These are respectively 800r (LD₅₀/30 days)(2) and 2 mg per kg (LD₅₀/14

days).(3) The 0.1% solution of nitrogen mustard was injected immediately after the crystals were completely dissolved in view of the instability of the compound. Eighteen rabbits were injected intravenously with 2 mg per kg nitrogen mustard. Eleven rabbits were killed at the following intervals: 30 min.; 3 hr; 8 hr; 16 hr; 24 hr; 3 days, 5 days, 10 days, 21 days, 6 weeks and 2 months. After the first 4 animals were killed, 7 of the remaining 14 died within 14 days after the injection. This indicates that the given dose was in the range of the LD₅₀ for this group of animals. The lymphatic nodules of the mesenteric lymph node and the appendix were studied.

The sequence of events in the lymphatic nodule of the mesenteric lymph node of the rabbit after nitrogen mustard is essentially identical with that after irradiation with the LD₅₀ dose. The destruction of lymphocytes leads to a nodule-free period beginning at 5 days and which terminates at 21 days when regenerative processes are present as evidenced by the formation of new nodules. Comparing the degree of regeneration with that after 800r of X-rays at the same interval, it appears that the regeneration is more advanced after nitrogen mustard. At 21 days there are larger and more new lymphatic nodules. These lymphatic nodules are at this time still without corona of small lymphocytes ("bare" germinal centers). A corona is present at 6 weeks and the regeneration is complete from then on.

In contrast to the changes in the mesenteric lymph node, the changes in the appendix after the LD₅₀ dose of nitrogen mustard are not comparable with those after an LD₅₀ dose of X-rays but they are similar to the results after the lower dose levels (400r and less). There is no nodule-free period, but after the debris has cleared up, small groups of lymphocytes remain in the dense masses of reticular

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2. Hagen, Ch. W., and Sacher, C., *Plutonium Project Record*, National Nuclear Energy Series, Div. IV, 22B, 1947.

3. Unpublished data, Univ. of Chicago Toxicity Laboratory.

cells. Regeneration occurs from these remaining lymphocytes.

These observations indicate that the histologic effect of nitrogen mustard on the lymphopoietic system is qualitatively but not quantitatively the same as the effect of X-rays at the same level of general toxicity. The effects on the mesenteric lymph node differ only slightly, the difference being a somewhat earlier regeneration. The difference is greater in the lymphatic tissue of the appendix. This lymphatic tissue shows changes after nitrogen mustard at the LD₅₀ comparable to the changes of the X-rays with a dose of half the LD₅₀. The findings of Jacobson *et al.*(4) demonstrating the more rapid regeneration of the rabbit bone marrow after nitrogen mustard as compared to X-rays and the findings reported here, seem to warrant the conclusion that the hematopoietic system regenerates in general more rapidly after nitrogen mustard than after X-rays with dose levels of the

same general toxicity, keeping in mind local differences such as are reported here for the mesenteric lymph node and the lymphatic tissue of the appendix. We have no definite explanation for these local differences. They may be based on differences in sensitivities of the lymphocytes, but it may also be that the instability of the compound *in vivo* causes differences in the effective concentrations in different organs.

Summary. The histologic effects on the lymphatic nodules of the rabbit after X-rays and after nitrogen mustard are identical in nature. However, there is a quantitative difference in the response of the lymphatic nodules to the LD₅₀ dose of the two agents. The difference is minor in the mesenteric lymph node, where there is a slightly earlier regeneration after nitrogen mustard than after X-rays. The difference is greater in the appendix where the histologic changes after nitrogen mustard at the LD₅₀ dose level are comparable to the changes after half the LD₅₀ dose of X-rays.

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Effect of Cortisone on Production of Granulation Tissue in the Rabbit.* (17555)

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Since Hench and his co-workers(1) demonstrated the dramatic therapeutic effect of cortisone and adrenocorticotrophic hormone (ACTH) in rheumatoid arthritis, numerous

investigators have found that these agents exert beneficial effects in a great array of disorders. These include such "mesenchymal diseases" as rheumatic fever, lupus erythematosus disseminatus and periarteritis nodosa. (2-4). The mechanism by which therapeutic

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