

HISTOPATHOLOGICAL CHANGES IN THE CENTRAL NERVOUS SYSTEM IN DOGS AT LATE PERIODS AFTER REPEATED WHOLE-BODY IRRADIATION WITH X-RAYS

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 51, No. 3,
pp. 106-110, March, 1961

Original article submitted May 4, 1960

The information in the literature concerning the morphological changes in the central nervous system at late periods after the action of ionizing radiation is scanty and is concerned mainly with animals surviving acute radiation sickness caused by whole-body x-ray irradiation in doses of 500-600 r [2, 3, 5] or local irradiation of the brain [4, 6].

In the present communication we describe the results of a histological study of the brain in ten adult dogs aged from four to six years, at late periods after prolonged, whole-body irradiation with x-rays in a daily dose of 20 r.

EXPERIMENTAL METHOD

Standard conditions of irradiation were used: voltage 180 kv, current 15 ma, filters 0.5 mm Cu + 1 mm Al, focus distance 140 cm, dose rate within the range 2-3 r/min. The first group consisted of three dogs (two of which received a total dose of irradiation of 500 r over a period of 25 days, and one received 600 r over a period of 30 days).

The second group consisted of seven dogs irradiated in two cycles separated by an interval of 11-12 months, and receiving a total dose of 1100 r. The duration of the first cycle of irradiation was 25 days, and that of the second cycle 30 days. The dogs of the first group, which were in a comparatively satisfactory condition (with no visible clinical signs of radiation sickness), were sacrificed 2.5 years after the cessation of irradiation, and the dogs of the second group, also in the same condition, were sacrificed three years after the end of the first cycle of irradiation and two years after the end of the second cycle.

According to Belousova [1], who made clinical observations on dogs in the course of irradiation (reaching total doses of 200 r and more), the animals showed certain signs of radiation sickness (lethargy, loss of appetite; in some dogs there were petechial hemorrhages on the skin of the dorsum, the abdomen and the oral mucosa). Belousova points out that after the cessation of irradiation the clinical signs disappeared and the dogs were in no way distinguishable from healthy animals in their external appearance.

Our object was to study the reactions of the central nervous system of dogs to prolonged whole-body irradiation in small doses* by means of histological methods. All the divisions of the brain were accordingly investigated histologically.

Sections were made by embedding pieces of the material for investigation in paraffin wax, and also by means of the freezing microtome, and were stained with hematoxylin-eosin, cresyl violet by Nissl's method,

*Dogs from Belousova's series of experiments.

and picrofuchsin by Van Gieson's method; the myelinated nerve fibers were stained by the method of Sokolyanskii and Veil'.

EXPERIMENTAL RESULTS

The results of histological investigation of the brain revealed pathological changes in the vessels, the nerves and the glial elements in all the dogs. The intensity and distribution of the structural disturbances in the tissues depended on the total dose of irradiation. For example, although the pattern of histological changes in the structures of the brain tissue were of the same character in the dogs of both the first and second groups, these changes were more severe and widespread in the dogs irradiated in two cycles and receiving a total dose of 1100 r.

The characteristic signs of the pathological changes in the brain tissue of all the animals were as follows: slight fibrosis of the pia and arachnoid in the dogs of the first group, and more marked fibrosis in the dogs of the second group, fibrosis of the stroma of the vascular plexuses, initial stages of proliferation of the collagen fibers in the walls of certain vessels, mainly in the brainstem. A moderate perivascular edema was detected, with edema in places beneath the ependyma of the ventricles, pyknosis and occasionally vacuolation of the nuclei of the endothelium and other cellular structures of the vessel wall.

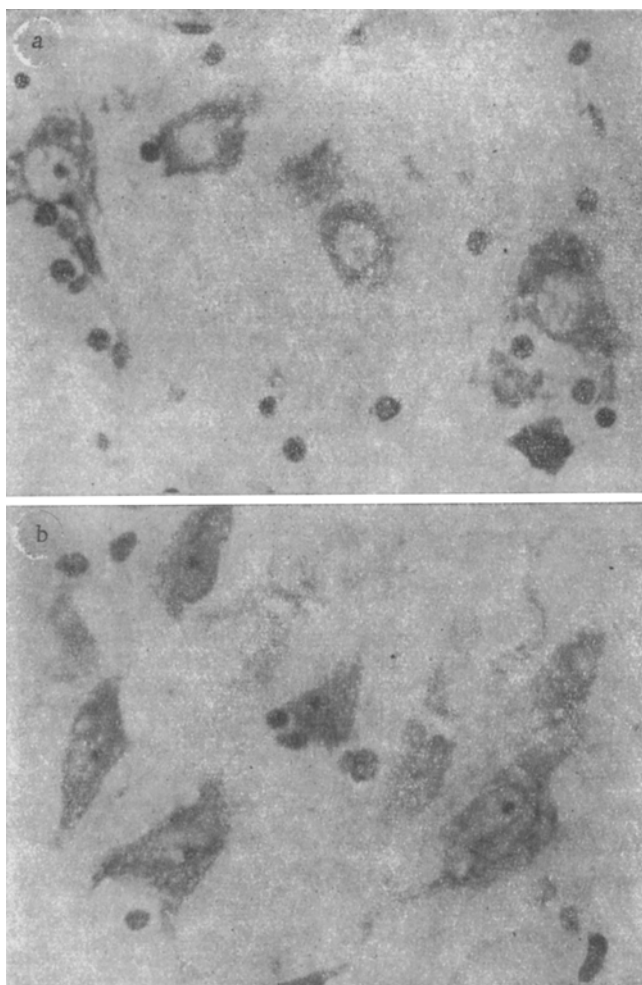


Fig. 1. a) Swelling of the nuclei of the nerve cells of the cerebral cortex in a dog. Magnification 400 \times ; b) edema and vacuolation of the cytoplasm of the cells of the deeper layers of the cortex. Stained with cresyl violet by Nissl's method. Immersion $\times 10$.

The changes in the nerve cells were characterized by selective involvement of the nuclei of the nerve cells of the cerebral cortex, the subcortical grey ganglia and the diencephalon, which were arranged eccentrically and swollen (Fig. 1). When gross swelling of the nuclei was present, atrophy of the cytoplasm of certain cells was observed. Nerve cells with vacuoles in their cytoplasm and with pericellular edema were found in all parts of the brain. In the deeper layers of the cerebral cortex vacuolation of the nerve cells was fairly widespread.

The diversity of pathological forms of cell involvement was found in all divisions of the brain: for example, side by side with hydropic degeneration of the cells others became shriveled, especially in the second layer of the cortex (in the unirradiated dogs the cells of the second layer of the cortex were almost as a rule more darkly stained than the other cells, but their structure was clearly defined). Shriveling of certain nerve cells was found in the dogs of the second group in the subcortical grey ganglia, in the supraoptic nucleus, less often in the periventricular nuclei of the hypothalamus, in the vegetative and afferent nuclei, and also in the reticular formation of the brainstem. Attention must be directed to weakness of the staining and the well marked reticulation of the intercellular substance. Around the circumference of the nerve cells were seen drainage forms of oligodendroglia, corresponding to the picture of cerebral edema. In the subcortical grey ganglia, especially in the caudate nucleus, in all the animals the cytoplasm of many cells stained very weakly with cresyl violet. The nuclei of such cells were slightly swollen, and some of them appeared "bare," evidently because of lysis of their cytoplasm.

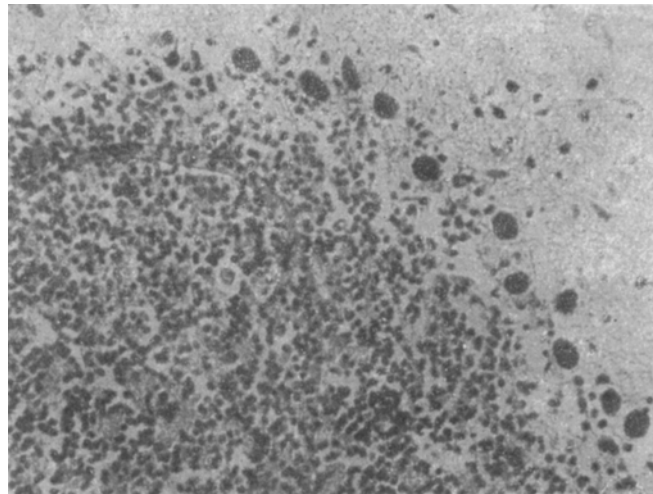


Fig. 2. Cerebellum. Shriveling of Purkinje cells and of certain nuclei of cells of the stratum granulosum. Stained with cresyl violet by Nissl's method. Magnification 400 \times .

It must be pointed out that the motor neurons of the brainstem were affected to a lesser degree. The most pronounced changes in the effector formations of the brainstem were observed in the cells of the inferior olives and in the Purkinje cells of the cerebellum. The predominant picture in the inferior olives was of shriveling of the nerve cells and death of these cells over a wide area. So far as the Purkinje cells are concerned, their pathology revealed great polymorphism, which evidently reflected the dynamics of involvement of these cells. The initial stages of the changes in the Purkinje cells took the form of hyperchromatosis of the nuclear membrane and lysis of the tigroid substance. The cytoplasm of certain cells showed vacuolation. Here and there pericellular edema was found, with shriveling of certain cells and karyocytolysis — the presence of cell-shadows (Fig. 2). Silver impregnation by Bielschowsky's method showed changes in the basket-like pericellular apparatus of the Purkinje cells.

Pathological changes were also found in the myelinated nerve fibers. In some preparations these were weakly and diffusely stained. Here and there scattered areas of demyelination, swelling and vacuolation of the nerve fibers (Sokol'yanskii's method) were found. A more obvious, and in some preparations an almost diffuse demyelination of the white matter of the brain was revealed by staining by Veil's method (Fig. 3). On the

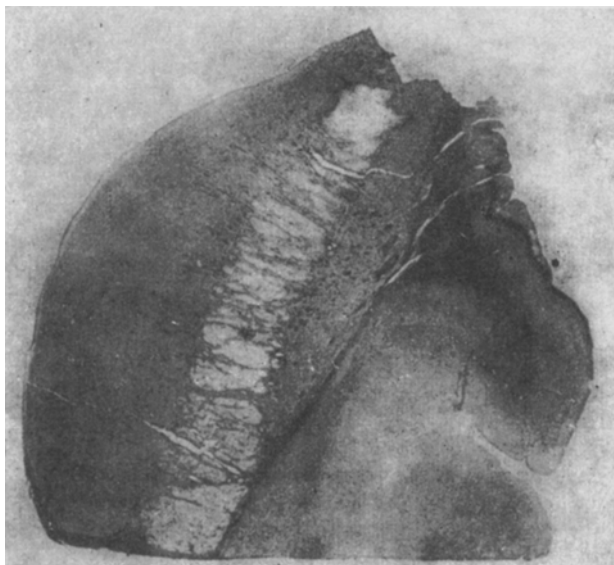


Fig. 3. Demyelination of the fibers of the anterior limb of the internal capsule. Survey preparation. Stained by Veil's method.

other hand, in preparations of the brain of unirradiated animals, stained by Veil's method, we sometimes observed only solitary foci of demyelination in the white subcortical matter.

The results of the histological study of the brain of dogs at late periods after the termination of prolonged irradiation in a daily dose of 20 r show that in dogs the absence of any outwardly obvious clinical disease is temporary, and is evidently due to the ability of the structures of the brain tissue to compensate for a long time their functions. The histological findings, however, reveal the progressive development of pathological changes in the pia and arachnoid, the vascular plexuses and the nerve structures. An indication of the progressive development of the pathological process in the brain tissue is the presence of different stages of the changes which were found. The selective character of the lesion of the neurons is gradually obscured, and other structures are involved in the process. A relationship exists between the development of the pathological changes in the brain and the total dose of irradiation. For example, well marked and widespread changes took place in the dogs receiving a total dose of irradiation amounting to 1100 r (dogs sacrificed two years after the termination of the second cycle of irradiation and three years after the termination of the first cycle). It must be pointed out that there is a definite similarity between the character of the lesion of the central nervous system in the dogs after prolonged irradiation with small doses and that in dogs surviving acute radiation sickness after a dose of 600 r [2, 3]. The character of the pathological process in the central nervous system bears the features of dystrophic disturbances, due not only to a disturbance of the circulation, but also, evidently, to histotoxic factors.

The histopathology of the brain as described by us in dogs at a period when clinical evidence of radiation sickness was absent raises a series of questions concerning the compensatory and adaptive mechanisms brought into play in radiation injuries, and also the influence of the changes thus found on the internal environment of the body. These questions are of great importance for an understanding of the role of the central nervous system in the pathogenesis of radiation sickness, and they demand special examination.

SUMMARY

Dogs were sacrificed at the period when no clinical signs of radiation injury were present. However, histological data demonstrated fibrosis to develop in the following areas of the brain at remote periods following total replexis of cerebral ventricles and in some vessels of the brainstem; changes of dystrophic character were seen in the nerve cells and in the myelinate nerve fibers. There was a certain relationship between the intensity and the extent of pathological changes in the brain and the sum total irradiation dose (the changes were more marked in dogs receiving the sum total dose of 1100 r). The data obtained lead to a conclusion that the clinical well-being of the animals is of a temporary nature, evidently being caused by the ability of brain structures to prolonged functional compensation.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
