CERTAIN PECULIARITIES OF NERVE TRUNK REGENERATION IN RELATION TO THE PHASE OF ACUTE RADIATION LESION

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The study of the process of regeneration of peripheral nerves against a background of acute radiation sickness which has been made by a number of authors [2-7, 10, 12-15] is of considerable theoretical and practical importance. However, this problem cannot be considered fully solved.

The purpose of this work was to study the regeneration of nerve trunks in relation to the phase of acute radiation sickness in an experiment on animals.

EXPERIMENTAL METHOD

Two series of experiments were exposed to a single dose of total-body irradiation on the RUM-3 apparatus (0.5 mm Cu and 1 mm Al filter, voltage 180 kV, current strength 10 mA, skin focal length 120 cm, irradiation time 3 h), total dose 350 r. Immediately after irradiation the right sciatic nerve of the dogs was transected at its middle third and after 2 h the segments were connected by 2-3 Capron epineural sutures.

The animals of the second group were also irradiated, but the nerve was transected and sutured 7 days after irradiation, i.e., at the climax of radiation sickness.

A dose of 350 r caused acute radiation sickness of average severity, rarely led to death of the animal, and made it possible to prolong the observation period. The dogs were killed at various periods (from 1 day to 1 year). The material for the investigation was gathered 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 360 days after the operation.

We investigated histologically the central segment of the nerve, region of the suture, peripheral segment of the nerve over its entire course, the sciatic nerve on the unoperated leg, the gastrocnemius muscles of both legs, the appropriate segments of the spinal cord, and the spinal ganglia. The material was fixed in a 12% solution of neutral formalin. The sections were stained with hematoxylin-eosin, Scharlach red, impregnated with silver after the Bielschowsky-Gros and Campos methods, stained for myelin by Spielmeyer's and Zolovova's methods. The spinal cord and spinal ganglia, furthermore, were treated by Nissl's method.

The degree of severity of radiation sickness was judged by the clinical picture, changes of the peripheral blood, and other indices.

EXPERIMENTAL RESULTS

Most radiated dogs became sluggish and lost their appetite as early as the first hours after irradiation. The peripheral blood on the day 1-2 postirradiation revealed moderate leukocytosis (11,500-13,200) and after 3-4 days there was a slight leukopenia (3500-4000) with a slight decrease in the number of reticulocytes and lymphocytes. After the same amount of time, the general state of the animals improved and their appetite returned. On the 6-7th day, the general state markedly deteriorated: the reaction to external stimuli became flaccid, appetite markedly dropped even to the complete refusal of food. Many animals developed diarrhea, and in certain cases mucus and blood were found in the feces. The body temperature rose to 40-40.5, and in rare cases to 41.5°. The animals

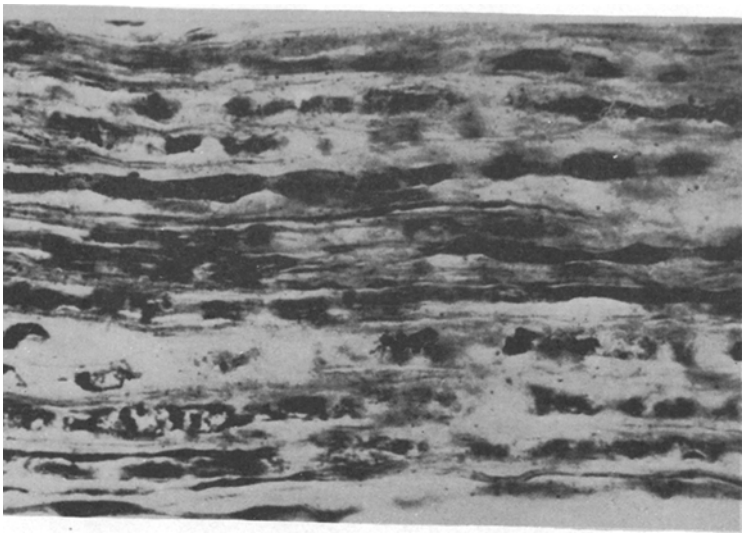

Fig. 1. Peripheral segment of sciatic nerve ten days after the operation performed during the latent period of radiation sickness. Fragmentation and disintegration of axons. Campos silver method. Objective 40x, ocular 7x.

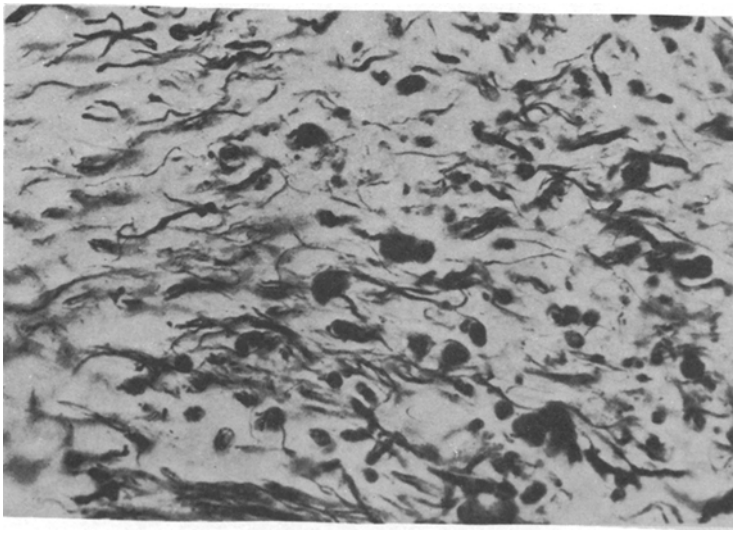

Fig. 2. Neuroma with multiple "inhibited bulbs" 20 days after the operation performed at the climax of radiation sickness. Campos silver method. Objective 20x, ocular 7x.

quickly lost 10-12% of weight. Most frequently by this time the foot and shank of the operated leg of the dog was markedly swollen. Later at the place of the swelling and edema, most frequently in the region of the toes and other portions of the extremities, alopecia and erosion appeared, which later changed to trophic ulcers.

In the animals operated on at the climax of radiation sickness, the number of leukocytes in the peripheral blood reached 800-1200. In certain of the dogs keratitis, nosebleeds, and hemorrhage into the palatal mucosa occurred and the hair fell out. Trophic ulcers in these animals were somewhat larger and granulated more slowly. In certain cases trophic ulcers appeared on symmetric portions of the unoperated leg.

As innervation was restored the external manifestations of trophic disorders lessened and a gradual epithelization of the trophic ulcers occurred. Keratitis, nosebleeds, dyspeptic disorders, and other manifestations of acute radiation sickness usually diminished and completely disappeared by the 30-55th day; trophic changes were retained

appreciably longer (50-80 days) especially in animals operated on at the climax of radiation sickness. In the dogs of the first group the ulcers granulated somewhat earlier. A month after the operation the number of leukocytes in the peripheral blood of the animals of both groups varied within 3700-6000, and in certain cases reached 9200. Usually by this time the animals of both groups willingly ate, gained weight, their body temperature became normal, they reacted lively to external stimuli, and rather rapidly ran about, limping or favoring the operated leg. Restoration of skin sensitivity occurs somewhat later in the dogs operated on at the climax of the disease.

During the first 5-10 days postoperation most of the known fibers of the peripheral segment of the nerve over its entire length in the animals of the first groups was in a state of disintegration and fragmentation (Fig. 1).

In the central segment of the nerve fine regenerating axons appeared as early as the third day postoperation. Only incipient signs of Wallerian degeneration were noted after 5-10 days in the dogs operated on at the climax of radiation sickness.

In the central segment we noted individual, newly-formed fibers. On the side opposite the operation no particular changes were noted in the sciatic nerve. In individual nerve cells of the spinal ganglia we detected dispersion of Nissl substance, hyperchromatism. The nuclei of certain neurons were situated eccentrically. In the animals operated at the climax of radiation sickness, these phenomena were somewhat more pronounced, certain neurons were hydropically altered. No great difference was elicited between cells of the left and right spinal ganglia. In the specimens of the spinal cord of the animals of both series we were not able to demonstrate any special changes.

By the 15-20th day the nerve fibers of the peripheral portion of the nerve segment in the dogs of the first group were in a state of profound disintegration and fragmentation. Young fibers, proliferating the region of the scar, were already noted in the peripheral segment of the nerve 1.5-2 cm distal of the site of transection. In the animals of the second group rather large neuromas had formed as a rule in the region of the scar. Some of the regenerated axons of the central segment of the nerve, having grown into the peripheral segment, enveloped the neuroma, others having grown into it spread out in different directions. Many of them curved spirally, grew in the opposite direction, and had "inhibited bulbs" on the ends (Fig. 2). The process of degeneration were appreciably slower in comparison with those of the animals operated during the latent period of radiation sickness (Fig. 3). Regeneration in the animals of this group was slow, fewer newly formed fibers were noted, and they were thicker and shorter. Some of the nerve fibers of the sciatic nerve on the unoperated leg were hyperimpregnated and varicosely altered.

On the 30-45th day after surgery the picture of the structural changes of the nerves in the animals of both groups became similar. However, in the dogs operated at the climax of radiation sickness the manifestations of retrograde degeneration in the central segment were more markedly evidenced, the neuromas were larger and distinguished by an appreciable density. A large bundle of young axons grew through the region of the suture into the peripheral segment of the nerve over a length of 3-5 cm. Neuromas of the dogs of the first group were found more rarely and were evidenced to a lesser degree.

On the contralateral side the axis cylinders of certain nerve fibers of the sciatic nerve were hyperimpregnated or varicosely altered. Retrograde changes increased in the nerve cells of the spinal ganglia in animals of both experimental groups. A number of neurons of the ventral horns and intermediate zone of the spinal cord was hyperchromatic. In certain of them the Nissl substance was in a state of diffuse chromatolysis. The nuclei of some of the neurons occupied an eccentric position. In certain cells we found vacuoles. The changes were expressed to the same degree on the right and left.

Whereas in animals of the first group the degenerative processes had mainly ended by the 60th day postoperation, in the dogs of the second group these processes were somewhat prolonged (sometimes up to 90 days and more). Most newly formed nerve fibers in dogs of both groups grew into the peripheral segment of the nerve as a thick bundle and were traced over its entire length. Certain newly formed nerve fibers underwent repeated degenerative changes. This was evidenced by numerous thickenings along the course of the fiber and fraying the fragmentation of individual axis cylinders.

No substantial difference was noted in the condition of the injured nerves in animals of both groups on the 180-360th day after the operation. The processes of degeneration and removal of products of tissue disintegration were completely finished. Over the entire length of the peripheral segment of the nerve we observed newly formed nerve fibers, primarily of average and large caliber, most of which were covered with a comparatively thin myelin sheath. In the muscles we noted motor endplates and sensory neuromuscular spindles. Only single hydropically

Fig. 3. Peripheral segment of sciatic nerve 20 days after the operation performed at the climax of radiation sickness. Fragmentation and disintegration of axis cylinders. Campos silver method. Objective 40x, ocular 7x.

altered neurons were encountered in specimens of the spinal ganglia. No changes were noted in the undamaged sciatic nerve and spinal cord.

The data obtained indicate that in acute radiation sickness of moderate severity the process of regeneration of nerve trunks is not disturbed but is only slowed down. This is especially noticeable at early periods of the experiments and can be explained by the direct influence of ionizing radiation which inhibits the processes of degeneration [1, 5, 8, 14] and by a number of other reasons associated with the development of radiation sickness [11].

In the dogs of the second group regeneration occurred later, evidently as a consequence of the fact that the combination of the climax of radiation sickness with disruption of innervation [9] and the formation of larger and denser neuromas in these animals hampered the proliferation of regenerating axons from the central segment into the peripheral.

At late periods of observations (120-360 days after surgery) no differences were noted in the condition of the injured nerves in animals of both groups.

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