HOW SECTIONING THE SCIATIC NERVE AFFECTS THE BLASTOMOGENIC ACTION OF STRONTIUM-89

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The use of radioactive isotopes with powerful cancerogenic action is a valuable method for the reproduction of tumors in order to study their pathogenesis, prophylactics and therapy. The isotopes selectively sorbed into the skeleton(Sr^{89}, Sr^{90}, Y^{91}, Ba^{140}, Ra^{226}), are known to produce primarily bone tumors, which are often localized in the tubular bones of the limbs [1, 3, 5, 6].

The role of physiological factors in the realization of radiation tumors has hardly been studied at all. The question of the role and importance of the nerve connections and their disturbance in the genesis of osteosarcomas has not been studied at all. This fact prompted the authors to take on the task of examining the influence of peripheral innervation on the blastomogenic action of radioactive strontium-89.

EXPERIMENTAL METHODS

Thirty-eight white rats, weighing an average of 145 g, were used in the experiment. A radioactive isotope-strontium-89 – was injected intraperitoneally in a dose of 77 microcuries per rat (0.53 microcuries per g) in a volume of 0.5 ml. Denervation of the right or left hind leg was done in all of the rats on the day of the isotope injection by transecting the sciatic nerve and removing 2-3 cm of it. X-ray pictures were taken twice during the experiments (on the 180th and 262nd days) in order to find any osteosarcoma development as soon as possible. In some of the dead animals, the strontium content in the femur and the tibia of both the denervated and the nondenervated leg was determined.

EXPERIMENTAL RESULTS

The average life duration (LV*50%) of the experimental animals, determined by the method of puncture-analysis (with constituent intervals for R*0.05), was about 190 ± 25 days when the rats were injected with 0.53 microcurie per gram of strontium-89.

In the majority of the rats, the skin atrophied and dystrophic ulcers developed in the region of the ankle joint of the denervated leg. Along with the atrophy and the thinning of the bony parts in the region of the metaphysis, a superfluous formation of bone tissue was sometimes observed in the denervated leg. Atrophic processes also developed in the hemopoietic tissue of the bone marrow of the denervated leg. The denervated bone marrow contained almost no hemopoietic cells, and the amount of collagenous fibers in its stroma increased considerably (Fig. 1).

Most of the animals (22 out of 38) unfortunately died before the 200th day, during the so-called "latent" period, necessary to the development of osteosarcoma. Bone tumors, therefore, only developed in a small number of animals. Malignant, osteosclerotic osteosarcomas developed in the leg with the intact somatic innervation of 3 out of 15 rats which died on the 247th, 286th and 316th day (Fig. 2 and 3, A); the tumors developed from the proximal epiphysis of the tibia in two rats and from the diaphysis of the femur in the third.

A bone tumor developed in the denervated leg in only one rat, which died on the 505th day. This tumor

* Transliterated. No explanation given in Russian text.

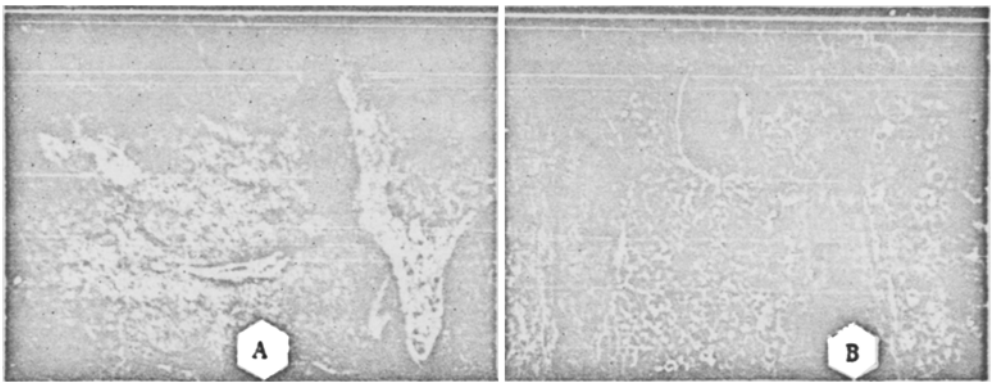

Fig. 1. A) Tissue of the denervated leg of a rat on the 90th day of the experiment with the injection of Sr^{89} (0.53 μ c/ g). Aplastic bone marrow. Massive thickening and sclerosis in the region of the metaphysis; B) tissue of the control leg with intact innervation. Hemopoietic bone marrow. Ordinary compact bone.

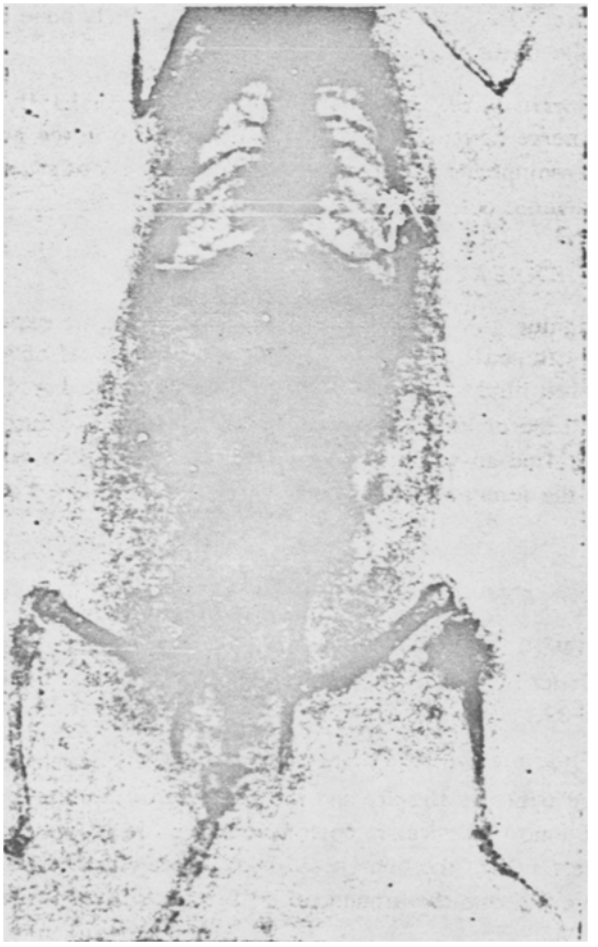

Fig. 2. X-Ray of rat on 260th day after Sr^{89} injection (0.53 μ c/ g). The rat died on the 286th day. Osteosarcoma of the proximal part of the tibia of the nondenervated leg.

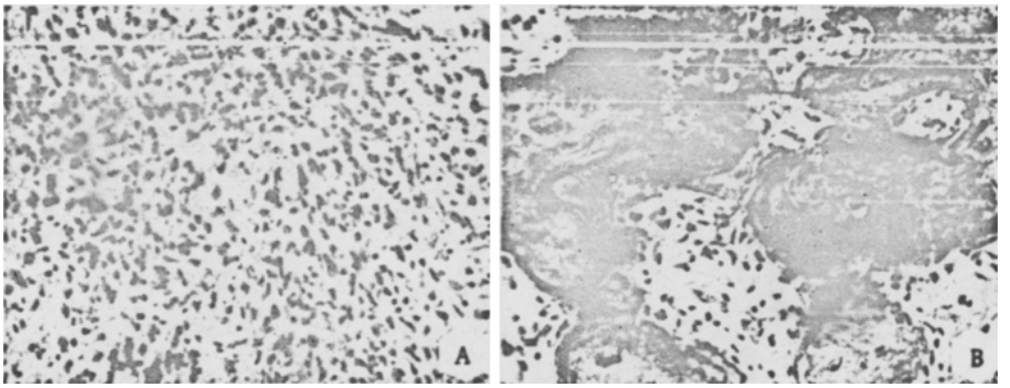

Fig. 3. Condition of tissue of a rat's leg in the experiment with the injection of Sr^{89} (0.53 μc/g). A) nondenervated leg on 316th day of experiment. Osteosclerotic sarcoma; B) denervated leg on 505th day of experiment. Osteosclerotic sarcoma.

not only developed later, but was in a place atypical for osteosarcoma — in the region of the ankle joint, where, for a long time, there had been an ulcerous affection of the skin and subcutaneous cellular layer. This tumor was a benign osteosclerotic sarcoma (Fig. 3,B).

The content and concentration of the strontium-89 was determined in the normal and denervated bones of the hind legs (femur and tibia) in some of the rats.

As the table below shows, the average content and concentration of strontium in the denervated femur was 24% and 14% lower than in the control. Analogous results were obtained with the tibia.

It was interesting to observe that the average weight loss of the denervated femur (10-15%) was more weakly expressed than the decrease in the strontium content (24%). This suggests that sectioning the sciatic nerve causes demineralization of the bone tissue as well as its atrophy.

The strontium content in the femur with the osteosarcoma was 50% higher than in the denervated and control femurs of the rats which died at the same time but did not have tumors, whereas the concentration of Sr-89 was considerably lower (3.5-3.7 times). The relatively lower content of strontium-89 in the denervated femur of rat No. 6) see Table), which was similar to the other denervated bones (according to decomposition per minute), was explained by the higher isotope content in the femur with the tumor.

This previous experiment indicates the important part played by the nervous system in the genesis of the tumorous process. One must mention that sectioning the sciatic nerve did not completely eliminate the ability of the bone tissue to react to the influence of tumorigenic agents, which is indicated by the benign osteosclerotic osteoma found in the region of the ankle joint on the 505th day. We must emphasize that, although we have observed a comparatively large amount of experimental material, including more than a thousand cases of tumor, this was the first time that we have observed the action of a radioactive isotope to cause a benign osteoma.

Let us turn to the unusual location of this tumor. As we have already observed, osteosarcomas ordinarily develop from the epiphysial region of the tubular bones. Evidently, a long unhealed, dystrophic ulcer of the skin and underlying tissues in the region of the ankle joint was the factor which, when combined with the action of the strontium-89 stimulus, gave rise to the benign osteoma.

Denervation appears to limit the blastomogenic reaction of bone tissue to the action of the specific stimulus of strontium-89. This conclusion is confirmed by the results of experiments recently conducted with cerium-144. These experiments showed that transecting and removing part of the sciatic nerve immediately after an injection of cerium-144 lowers the rate of osteosarcoma development in the denervated extremity by two times. The results obtained are known to agree with the observations of experimental and clinical oncology, which has long used the method of sectioning and removing nerves. For example, A. G. Molotkov [2], by sectioning the second branch of the trigeminal nerve, obtained, in some cases, rapid healing in skin cancer of the cheek and upper lip in humans. According to the observations of I. A. Pigalev [3], sectioning the vagus nerves hinders, but does not eliminate the development of gastric melanoadenomas.

Relative Content (in entire femur) and Concentration (per gram of wet weight) of Strontium in the Denervated Femur (in % of control)

No. exptl. animal	Time of rat's death	Content	Concentration
1	193	62 5	77 5
2	196	52 4	89 0
3	223	79 3	102 0
4	225	77 0	86 0
5	236	70 4	80 5
6	247*	58 1	344 0
7	273	67 4	69.6
8	291	79 6	93 2
9	311	81 7	83 5
10	338	84 2	92 2
Average amt. without rat No. 6.		76±2 5%	86 0±3 2%

* In the femur of the control leg of rat No. 6, an osteosarcoma was found; the weight of this femur was 6 times greater than that of the denervated one.

What is the explanation for the inhibition of osteosarcoma development in the denervated leg? It is certainly not due to any effect of denervation on the distribution of the radiator, since there was very little difference in the isotope content of the normal and denervated bones, and, moreover, osteosarcomas can develop from smaller doses of strontium as well. The comparatively rare development of osteosarcomas in the denervated leg is evidently connected with the general inhibition of growth and the preeminently atrophic changes of the bone tissue caused by denervation (atrophy and thinning of bony parts, lowered mineral salt content), which changes naturally hinder processes causing swift and uncontrollable cell growth, such as the tumorous process. Therefore, in the final analysis, the "favorable" effect of denervation is explained by its inhibiting influence on bone tissue growth and development.

SUMMARY

The role of sciatic nerve section on the blastomogenic effect of strontium-89 has been studied in albino mice. Three out of fifteen animals developed malignant tumors on the limbs with an intact somatic innervation. But only one animal developed a tumor on the denervated limb, on the place of an unhealing trophic ulcer. The tumor was a benign one, an osteosclerotic osteoma. The results could not be accounted for by any difference in the strontium content of the normal and denervated limbs since the difference was comparatively small.

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