ONCOLOGY

TUMOR OF THE BONE TISSUE INDUCED BY RADIOACTIVE SUBSTANCES*

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As has been established, ionizing radiation has a blastomatogenic property. Various types of "external" radiation (γ, x and β rays, neutrons) and radiation with radioactive elements entering the organism can lead in given conditions to malignant growth of that organ or tissue subjected to their influence. Thus, cancers and sarcomas of the skin, the tissues of the buccal cavity, and various internal organs in persons following therapeutic irradiation with x-rays and radium are known [3, 6, 14, 20 and many others]. In cases of deposit of radioactive elements in the organism, a malignant process usually develops in the organs and tissues accumulating these substances (lungs, bone system) or secreting them as, for example, the colon [11, 15, 16, 17, etc.].

The possibility of producing tumors of many organs and tissues by "external" radiation, or by the effect of radioactive elements entering the organism has been experimentally demonstrated. On these questions, extensive material has been accumulated and presented in detail in a number of reviews and monographs [2, 7, 14, 15, 21].

Recently much attention has been paid to the study of the possibility of the development of malignant turmors of the bone tissue with affections induced by radioactive substances. This is due to the fact that many radioactive elements possess the capacity of depositing and maintaining themselves for a long time in the bones (the majority of products of division of uranium, plutonium and other elements).

Martland was the first to describe the development of bone sarcomas in persons with radioactive substances deposited in the organism. Since then, many experimental papers have appeared in which the development of tumors of the bone tissue in various animals upon introduction of various radioactive elements – strontium, yttrium, cerium, zirconium, radium, plutonium, etc., has been described [7, 8, 9, 19, etc.]. Recently, these experiments have been reproduced in monkeys [1].

It is, however, necessary to say that many questions connected with the study of the development of tumors of the bone tissue under the influence of radioactive substances remain unexplained. There are no descriptions of the malignant process previous to the changes in the bone; the transitional "pre-sarcomatose" states have not been studied; there are no detailed descriptions and classifications of developing tumors; the "threshold" doses of radioactivity have not been clarified nor have the "latent" periods for the various radioactive substances, and so on.

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Having some experience in this field, we wish to draw the attention of investigators to the questions involved in the study of the development of malignant tumors of the bone tissue under the influence of radioactive substances. This problem may be of interest not only for radiologists, but also for specialists working in other fields.

Tumors induced under the influence of radioactive substances constitute a good and easily reproducible model for studying the processes of malignant growth of the tissues, the dynamics of malignant growth and for its subsequent investigation.

Tumors of the bone tissue upon introduction of radioactive substances fixed in the bones are most easily induced in rats. At given doses of radioactivity, the substance introduced in these animals regularly causes osteogenic sarcomas to develop in 6-8 months, in 40-80% of the cases. A very large number of animals (up to 80%) are afflicted with tumors upon introduction of radioactive strontium (Sr^{89} and Sr^{90}).

The radioactive substance in a small volume of physiological solution or distilled water is introduced orally, subcutaneously, intraperitoneally or intravenously. The most expedient route for rats must be considered to be the intraperitoneal method of introduction, since it is very simple and hence safe for the research worker, and requires relatively little radioactive substance.

We kept under observation some hundreds of rats which were given radioactive strontium (Sr^{90}) intraperitoneally in doses of 0.1, 0.2, 0.4, 0.8 and 1.6 μ C per 1 g body weight. In the largest percentage of cases tumors appeared in the rats which received the substance in a dose of 0.4 μ C per g. This dose should generally be regarded as optimal for reproduction of tumors [6, 8, 19, etc.]. With smaller doses (0.1 and 0.2 μ C) tumor in our experiments occurred much less frequently. With doses of radioactivity of 0.8 and 1.6 μ C per 1 g body weight, a picture of sub-acute or acute radiation affection was observed in our animals which died without developing tumors.

In the animals receiving the substance in a dose of 0.4 μ C per 1 g body weight, tumors developed in approximately 70-80% cases. However, these findings require elaboration since the majority of rats in our experiments were sacrificed (which was taken into account) at various stages after introduction of the substance in order to study the dynamic of change in the bone tissue and internal organs. In one group, consisting of 100 rats, tumors developed in 73 animals at periods from 180 to 300 days after introduction of the substance. These findings correspond in general to those presented in the literature.

Tumors appeared in the rats starting from the 180th day after introduction. In rare cases an earlier development of malignant growth was observed. The largest number of tumors appeared on the 200-250th day after introduction of the substance; they, as a rule, appeared in the metaphyses of the long pipe bones – of the tibias, femoral and shoulder bones. Plural development of tumors in various bones in the same animal was often observed. At first, 190-210 days after introducing the substance, in many rats there appeared tumors principally in the proximal metaphyses of the tibias and also in distal metaphyses of the femurs. Later, they began to arise also in the proximal metaphyses of the femurs and shoulder bones. Not infrequently the tumors developed in one animal simultaneously in different bones. Metastases in the lungs were often observed. A quantitative law applying here cannot be established since many rats were sacrificed (in order to study the dynamics of malignant growth) which still had comparatively few tumor nodes in one bone.

As is known, radioactive strontium, similar in its chemical properties to calcium, upon introduction in the organism deposits itself at sites of re-formation of bone substance [4, 5, 12, 13, 18, etc.]. In growing rats, these in the first place are the areas of the enchondral ossification of the long pipe bones. It is also necessary to take into account that in rats the largest growth in length, for example of the tibia bone, occurs on account of the proximal epiphysis, and in the femoral bone on account of the distal one [9, 10]. Therefore, one can with assurance postulate that the largest quantity of radioactive substance is accumulated precisely at these sites of particularly intensive bone formation.

The histological findings confirm this hypothesis. The most marked morphological changes are found precisely in the areas of growth of the long pipe bones, in the first place in the proximal metaphyses of the tibial bones, distal metaphyses of the femoral bones, and also in the proximal metaphyses of the shoulder and femoral bones. These changes culminate in disturbance of the process of enchondral bone formation and resorption of part of the re-formed bone substance with the development of cellular-fibrous tissue containing a large amount of osteoclasts.

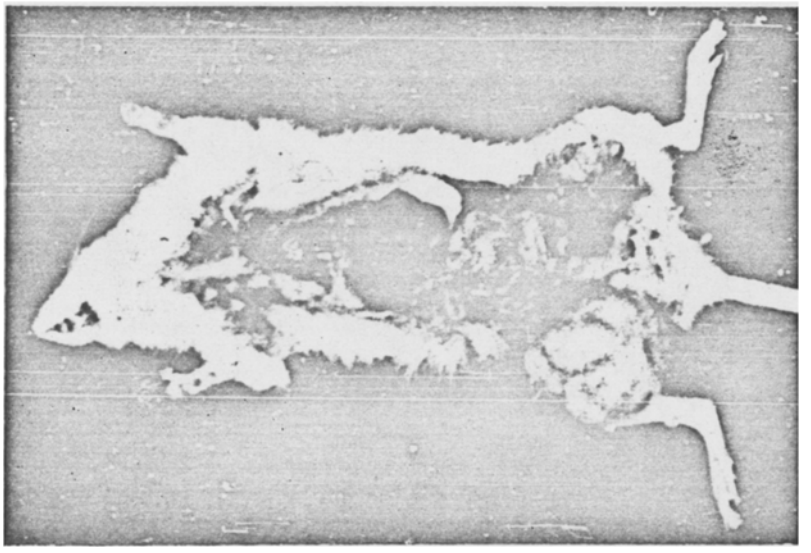

Fig. 1. External appearance of tumor of the right femoral bone, developing in rats 230 days after intraperitoneal introduction of radioactive strontium in dose 0.4 μ C per g.

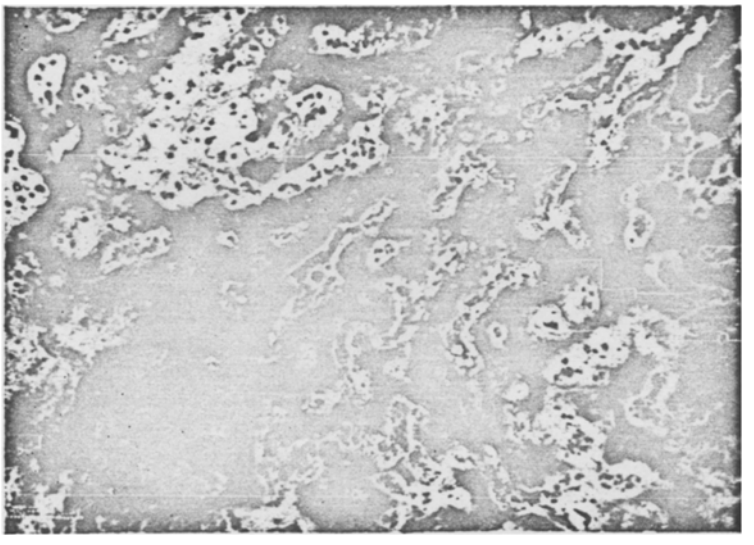

Fig. 2. Tumor emerging from femoral bone. Consists of atypical osteoblasts and poorly formed ravines of the osteoid substance. Microphotography.

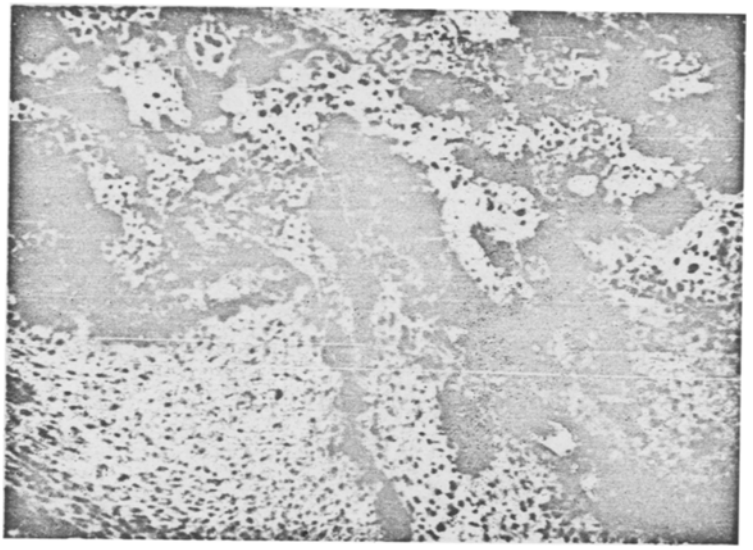

Fig. 3. Tumor of tibial bone. Together with immature bone tissue it is also composed of cartilageous and fibrose tissue. Microphotography.

Subsequently growth of the bone in length is slowed down and distorted. Formation of pathological bone substance occurs which does not undergo further rebuilding. In the metaphysis, around the remaining non-resorbed bone substance and newly formed pathological bone substance, there occurs growth of the cellular-fibrous tissue with formation of atypical immature bone substance, differing in appearance.

With the passage of time the processes of bone formation are increasingly disturbed. Sections of polymorph atypical osteogenic cells appear. They quickly multiply without producing basic bone substance. Then these tissue formations, having a tumor-like appearance, spread at the side of the epiphysis chondral blade filling the cavity of the metaphysis, and through the bone marrow to the side of the diaphysis. Usually penetration of the tumorous masses through the destroyed cortical substance of the metaphysis outside the bone takes place early.

The external tumorous growths often reach large proportions and have a spherical shape with a "bumpy" surface (Fig. 1). On incision into the tissue of the tumor, hemorrhages are visible with ulcerations on the surface. External tumorous nodes are usually covered with a connective tissue capsule. Tumorous growth does not spread to the neighboring bones.

Histologically the tumors have a varied and complicated structure. Their cellular elements represent productive osteoblasts and fibroblasts, and less often cartilagenous cells. Often polymorph distorted forms are also found. The basic substance represented by osteoid is partially calcinated with poorly formed bone substance, collagen and cartilage. Often the tumors in appearance resemble so-called osteoblastosarcomas (Fig. 2). However, almost always in their composition one can find fibrous tissue and accumulation of cartilage-like cells (Fig. 3). Occasionally the tumors approximate in structure to a polymorphocellular sarcoma; in a number of cases they resemble in appearance chondrosarcoma, fibrosarcoma, etc.

Thus, under the influence of radioactive substances in given conditions, one may experimentally obtain a model of tumors of the bone tissue which can conveniently be studied. The tumors develop at the site of the most marked morphological changes, peculiar to the given affection – in the metaphyses of the long pipe bones. Malignant growth is preceded by a long evolutive process of distorted bone formation with disturbance

of the mutual relations between resorption and re-formation of the bone and development of cellular-fibrose tissue, which undergoes characteristic changes.

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* In Russian.