EXPERIMENTAL OSTEOMYELITIS AND SOME PROBLEMS OF ITS PATHOGENESIS

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(Received June 26, 1958. Presented by Active Member AMN SSSR V. N. Chernigovskii)

Ideas of the pathogenesis of osteomyelitis were considerably developed by the research of S. M. Derizhanov [1, 2]. However, neither S. M. Derizhanov nor other workers using his technique in their research, studied certain fundamental problems of the pathogenesis of experimental osteomyelitis in sensitized animals; in particular, the importance of neurovascular disorders in the pathogenesis of this disease was not explained.

D. G. Rokhlin pointed out that in the study of the pathogenesis of osteomyelitis it is essential to take into consideration the important role of prolonged spasm of the vessels. In view of the anatomical and physiological peculiarities of bone, in certain immunobiological conditions this factor may have an essential effect on the development of the disease and may be responsible for its character. The type of sequestra depends on the peculiarities of the bone and on the site of spasm of the vessels.

The aim of the present investigation was to ascertain the importance of neurovascular disorders and, in particular, the role of prolonged spasm of the vessels in the pathogenesis of experimental osteomyelitis. In the work we, therefore, dealt with the following problems: 1) to reproduce experimental osteomyelitis in animals; 2) to make a detailed study, by means of x-ray examination, of the development of the osteomyelitic process and to associate the appearance of its different forms with particular disturbances of the blood supply of the bone; 3) to ascertain the role of prolonged spasm of the vessels in the pathogenesis of experimental osteomyelitis by the use of ganglion-blocking drugs.

EXPERIMENTAL METHOD

Experimental osteomyelitis was induced in rabbits by the method suggested by S. M. Derizhanov. In this series, experiments were performed on 68 animals — males and females weighing from 1800 to 2500 g. Twelve rabbits acted as controls, and 56 were given five preliminary sensitizing injections of normal horse serum, subcutaneously, in the hindlimb, in volumes of 2-3 ml and at intervals of 5 days. From 8 to 10 days after the last subcutaneous injection, 2-4 ml of horse serum was introduced through a drill hole directly into the medullary cavity in the middle part of the tibial diaphysis. This was the assaulting dose of horse serum. The same operation was performed on the control animals, but without preliminary sensitization. From 10 to 20 minutes after introduction of the assaulting dose, 18 of the 56 rabbits died from anaphylactic shock. None of the control animals died. The 38 surviving experimental animals and the 12 control animals were kept under observation for various periods of time.

EXPERIMENTAL RESULTS

Despite the fact that all the rabbits were kept under identical conditions, the experimental animals differed

greatly from the controls in their general condition. The disease was expressed clinically in these animals by an increase in the temperature, slight loss of weight, edema of the injured limb and the formation of an area of infiltration and erythema of the skin at the site of the operation wound. In the blood, the ESR was raised to 20-25 mm in 1 hour, and there was a fall in the hemoglobin concentration and a rise in the leucocyte count to 25,000 per mm^3. The control rabbits were clinically indistinguishable from animals not undergoing operation. Two weeks after introduction of the assaulting dose of serum into the marrow cavity, a systematic series of x-ray films was taken of both hindlimbs of each animal; at first once a week and then twice a month. Under these circumstances we directed special attention to the detailed recording of the pathological changes in the bone and to the course of their development. No osteomyelitis could be detected in any of the control animals. In the experimental animals, on the other hand, one of the forms of osteomyelitis, with an acute, subacute, or chronic course, was observed in all cases.

Analysis of the x-ray films showing the development of the pathological changes indicated that usually on the 20th-21st day, and sometimes earlier, changes appeared both in the soft tissues around the bone and in the periosteum, and also in the cortical substance and the marrow cavity. At this time, on the x-ray films it was possible to observe localized edema of the soft tissues at the level of the drill hole; sometimes the edema was more diffusely spread, affecting the entire limb below the knee. Depending on the character of the developing pathological changes, the edema of the soft tissues lasted for a long time or gradually diminished and completely disappeared.

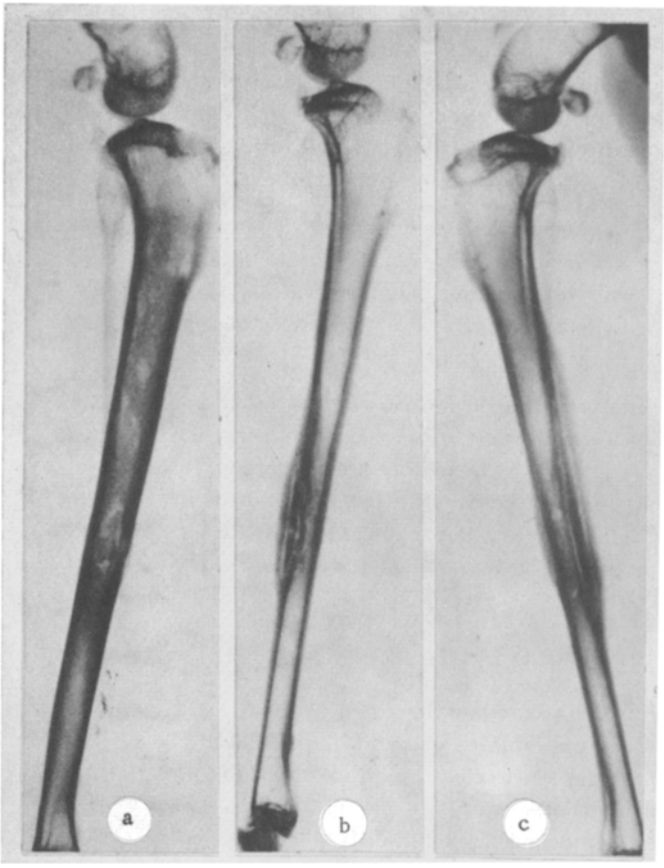

Fig. 1. Osteomyelitic and necrotic changes in the marrow substance in experimental osteomyelitis in rabbits.

On the x-ray films of the 20th-25th day a fine shadow of thickened periosteum appeared in the region of the drill hole, to some extent stripped from the compact bone. Subsequently these periosteal deposits increased in size; the bone was thickened either regularly or irregularly. In contour they were undulating, but smooth; however, in association with the passage of pus (in the presence of a sinus) the contours became, as it were, eroded.

The x-ray films at the beginning of the 4th week, or sometimes later, showed destruction of bone tissue, which took place not only in the region of the operation wound but also far from its limits. Sometimes the pathological process spread from the proximal to the distal metaphysis. Destruction was shown both by osteolysis and by the appearance of necrotic (from their x-ray appearance) areas of different sizes and shapes. At the end of the second month progression of the pathological changes was usually observed, and at the 4th month the lesion reached the peak of its development. The x-ray films at this period showed clearly the formation of sequestra, cavities and sequestral capsules, delineating the affected focus from unchanged bone. In other cases the acute inflammatory changes began to quiesce, and the entire process, becoming localized, acquired a chronic character. In addition to the appearance of cavities and sequestra, irregular sclerosis of bone was seen to develop both periosteally and endosteally.

In our experiments there were cases in which the changes were localized mainly in the periosteum, and the developing process terminated at the end of the 4th-5th month (the most favorable course). From the very beginning edema of the soft tissues was seen, and after 3 weeks stripping of the periosteum was seen in a localized

area of the tibial diaphysis at the level of the drill hole on the x-ray films. Two weeks later this process had spread considerably and the deposits under the periosteum had undergone partial assimilation. Occasionally the process terminated in complete assimilation of the subperiosteal deposits. In such cases the changes did not extend into the depth of the bone.

In certain rabbits the inflammatory process was localized, at a certain stage of development, to the subperiosteal layer of compact substance of the bone. It was very characteristic that, although it spread over a considerable part of the surface, it did not penetrate deeply and did not affect the supraspongiosal layer nor the marrow cavity. At later stages in some rabbits we observed sequestrum formation, the separation being confined to superficial areas of the subperiosteal layer of the compact substance of varying extent. The form of osteomyelitis described must be due to disturbance of the circulation of the blood in a restricted area of the periosteal network, since the subperiosteal layer of the compact substance is supplied by this system of vessels. According to D. G. Rokhlin [6] the supraspongiosal layer of compact substance and the medullary cavities are supplied with blood from the diaphyseal network.

In Fig. 1a, are shown multiple osteomyelitic and necrotic changes in the medullary cavity in the presence of destruction of only the supraspongiosal layer of the cortical substance, a feeble periosteal reaction and absence of any well-marked edema of the soft tissues.

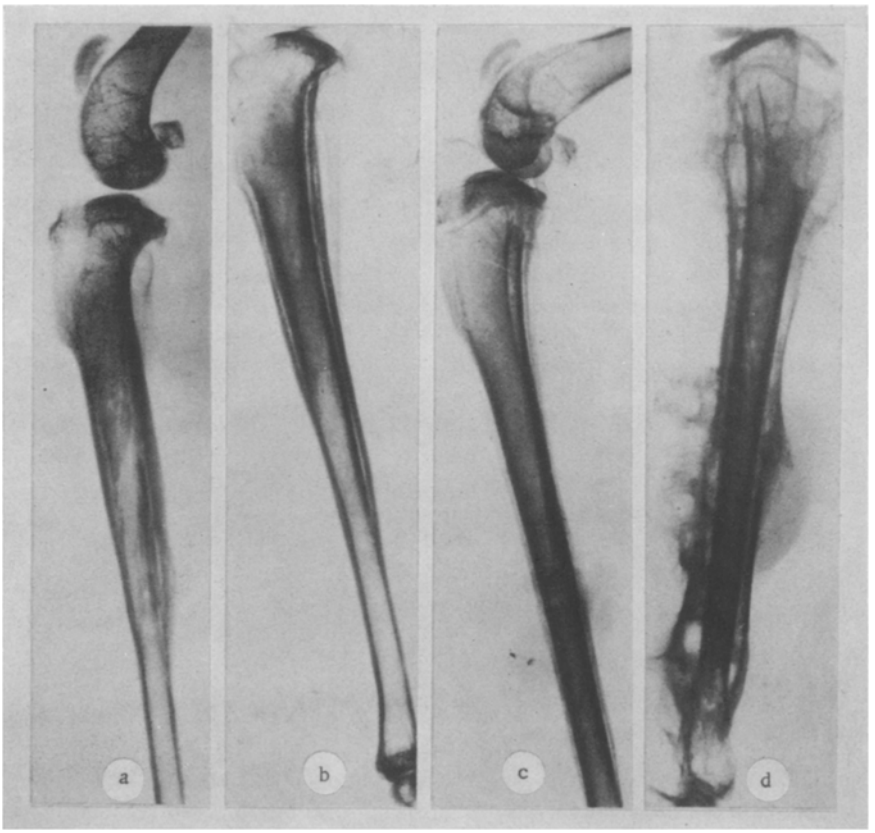

Fig. 2. Total central necrosis in experimental osteomyelitis in rabbits.

Conversion of the subperiosteal and supraspongiosal layers into long, rod-like sequestra at the level of the drill hole is readily seen in Fig. 1, b; osteolytic changes are also seen in a small area of the substantia spongiosa. The sequestra are covered externally by highly assimilated periosteal deposits.

Necrosis of the subperiosteal layer of the compact substance and partial osteolysis of the adjacent supraspongiosal layer, in the presence of intensive periosteal deposits are shown in Fig. 1, c. In this rabbit a pathological fracture occurred in the affected tibia at the junction of the middle and distal thirds.

A case of total central necrosis with pathological fractures in one of the experimental rabbits is demonstrated in Fig. 2, a. Well-marked assimilated periosteal deposits are observed on the posterior surface of the tibia. Total central necrosis, arising in other rabbits, is illustrated in Fig. 2, b. No clearly expressed periosteal changes are seen in the x-ray films in these cases. The development of pathological changes, as shown on later film, must be due to disturbance of the circulation of blood in the branches of the main diaphyseal artery supplying the marrow cavity and the supraspongiosal layer.

It was possible, experimentally, to obtain total necrosis of the bone, i.e., necrosis of the whole thickness of the bone. This was possible only by cessation of the blood supply from the diaphyseal and periosteal networks of vessles.

Fig. 2, c illustrates total osteomyelitis of the proximal $^2/_3$ of the tibial diaphysis. The whole extent of the area undergoing necrosis is surrounded by periosteal deposits. In Fig. 2, d is shown a case of severe chronic osteomyelitis with total necrosis and sequestration of the whole diaphysis of the tibia (from the proximal to the distal metaphysis). Pathological fractures are seen, together with extremely extensive periosteal deposits, in places doubling the thickness of the bone. Well shown on the x-ray films are multiple sinuses and also marked edema of the soft tissues.

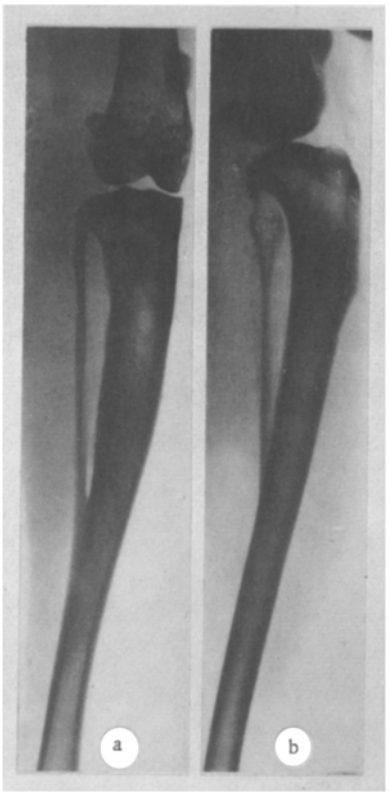

Fig. 3. Osteolysis of the substantia spongiosa (a) before and (b) after treatment of experimental osteomyelitis.

On the basis of the x-ray examinations we distinguished several different types of sequestrum formation in experimental osteomyelitis. These types or forms were mainly identified by considering the localization and duration of the process. The presence of different forms of osteomyelitis may be explained by disturbance of the blood supply—by prolonged spasm of the vessels in either the periosteal network or in the diaphyseal artery and its branches or in both.

Regarding the development of osteomyelitis in sensitized animals as the result of spasm of the vessels (D. G. Rokhlin), we attempted to discover, by the use of drugs, the importance of spasm of the vessels supplying the bone in the pathogenesis of the disease. In the experiments which we set up (on 70 rabbits), ganglion-blocking (spasmolytic) substances — hexamethonium, trasentine — were injected in therapeutic doses calculated per kg body weight, immediately or 1-2 hours after the assaulting injection and thereafter 2-3 times daily for 6-20 days. Control rabbits received no injections of ganglion blocking drugs. The development of osteomyelitis in the rabbits of the control series and the animals receiving ganglion-blocking drugs was systematically followed by x-ray examination for 6 months.

As a result of the observations it was found that in the control rabbits, which received no injections of these spasmolytic drugs, osteomyelitis developed in 100% of cases (with one or other type of sequestration). In the rabbits which were injected with hexamethonium or trasentine osteomyelitis failed to develop in 90% of cases.

After obtaining these results, we used ganglion-blocking drugs for therapeutic purposes. We utilized some of the rabbits of the control group in which an osteomyelitic lesion was found. As an illustration we give the following example of hexamethonium treatment of a rabbit which had already developed osteomyelitis. In Fig. 3, a, osteolysis of the substantia spongiosa in the proximal third of the diaphysis of the bone and tiny necrotic areas in the substantia spongiosa may be seen radiographically. As a result of osteoporosis, the compact layer in the proximal metadiaphyseal zone cannot be traced along the posterior surface. Fine, undulating periosteal deposits may be seen over a rather extensive area. Two months after the beginning of treatment with hexamethonium, the bone of this rabbit was normal in structure, which had undergone complete restoration (Fig. 3, b). Similar results were obtained in other animals. These findings support the view put forward by D. G. Rokhlin, that spasm of the vessels is important in the pathogenesis of osteomyelitis. It seems to us that they open up wide prospects for the use of ganglion-blocking drugs in the prophylaxis and clinical treatment of osteomyelitis, used in conjunction with all the measures which are at present employed.

SUMMARY

Several typical forms of experimentally induced osteomyelitis were obtained in 68 rabbits by Derizhanov's method. X-ray examination demonstrated that the pathological process was localized in the periosteum or in various layers of the compact bone substance. Total necrosis was revealed in certain cases. In conformance with the belief that there is a separate blood supply of various layers of the compact substance of long bones a conclusion is drawn that a varying localization of the process is associated with disturbances of the blood supply in certain blood vessels.

A prolonged spasm of the blood vessels plays, apparently, the main role in the disturbance of the blood supply of the bone.

The author studied the significance of spastic manifestation in the vessels by attempting to prevent as well as to treat the initial stages of osteomyelitis with the aid of repeated administration of hexamethonium and trasentine. Administration of ganglion-blocking substances prevented the development of osteomyelitis in 90% of cases. The osteomyelitic process was controlled in a number of instances. The results demonstrate the importance of the vascular spasm in the pathogenesis of experimental osteomyelitis.

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