TEACHING EDITORIAL

Radionuclides in the Diagnosis of Fracture Healing

The study of fracture healing is ultimately directed toward a better understanding of delayed healing and nonunion, both of which are complications of normal fracture healing. In long-bone fractures, delayed healing or nonunion is difficult to diagnose, and trials of operative management and observation have become routine. Radiography is at present the only non-traumatic diagnostic test commonly used to monitor the healing process of a fracture. The results are often inconclusive.

A number of different bone-seeking radiotracers have been shown to accumulate progressively over a fracture, reach a plateau, and then gradually decrease as healing is effected. Longitudinal studies using a single tracer injection (*1*), multiple injections (*2*), or daily injections in rats (*3*), each of these combined with external probe counting, have shown that no reliable separation between normal and complicated fracture healing can be achieved. Part of the problem is that studies in patients are difficult to interpret, because healing depends on the blood supply of the bone fragments, the type of fracture line, the injury to associated tissues, and the integrity of the periosteal envelope, all of which are difficult to control in human fracture studies. Besides, a single injection of a bone-seeking radiopharmaceutical may not be satisfactory for the study of such a complex process as fracture healing. Repeated injections in patients, however, are restricted by the few times one can justifiably apply a radioactive nuclide. Radiation doses that are known to affect bone healing negatively (*4*) would not be reached, but radiation to target organ and gonads would limit the acceptable number of studies.

Good animal models have been developed for the study of normal and abnormal fracture healing (*5,6*). Such studies have generally used histologic, microradiographic, and autoradiographic techniques, all applied to excised bone tissue. Again, however, external counting after single or repeated injections of bone-seeking or blood-pool-labeling radionuclides has not been successful in reliably separating normal from abnormal fracture healing (*7*).

Progress in this direction has been made, however, by following the healing of bone grafts with imaging techniques. Here the uptake by the graft can be compared with that of the surrounding bone (*8*). This has resulted in more specific information than can be obtained from counting methods that make use of external probes.

Gumerman and colleagues, in this issue of the *Journal,* have demonstrated that the new quantitative radionuclide imaging techniques are applicable also to bone-fracture healing and can lead to more specific information and perhaps to the recognition of uptake patterns characteristic of normal and abnormal fracture healing (*9*). It is currently too early, however, to speculate about the usefulness of this pattern-recognition approach for the diagnosis of fracture healing in man. The significance of these patterns would best be tested further in the animal model with the use of factors that are known to affect bone healing.

Diagnostic patterns should correlate with the anatomic and physiologic changes they are designed to indicate. The following is a review of the bone-healing process in the animal model (*10,11*). About 4-8 hr after the fracture, the bone defect is filled and is surrounded by extravasated blood, hemorrhagic debris, and inflammatory exudate, which produce the procallus. At 24 hr there is formation of connective tissue, initially granulation tissue, which then continues to proliferate and form dense, fibrous connective tissue. A part of this tissue differentiates further to form hyaline cartilage and fibrocartilage and produce the fibrocartilaginous callus. By the third day after the injury, the initial blood clot is replaced by this tissue. The size of the callus replacing the procallus and the amount of cartilage included depend to a large degree on

the extent of the initial injury, the amount of trauma to which the site of fracture is subsequently exposed, and the age and species of the animal.

Simultaneously, ossification begins away from the fracture line, originating from the deep layers of the periosteum and endosteum. At points where osteogenous cells happen to grow in well-vascularized surroundings, they change into osteoblasts, whereas at points where vascularization is less abundant they become chondroblasts. Thus the membranous bone is calcified as it is laid down. Under optimal conditions, uncalcified osteoid is seen sparingly. Next, the bone advancing from both sides toward the fracture line surrounds and invades the fibrocartilaginous callus and starts the process of ossification in this area.

The parts of the bone fragments that are adjacent to the fracture line are necrotic, and they become surrounded by macrophages and foreign-body giant cells as early as 4 days after the fracture. As a consequence, these parts of the fragments become porous, and this creates the impression of the "atrophy of the cortical ends" known from radiographs. Finally, bony union is established, and the fracture site is bridged.

The successful organization of the preliminary callus and its further development are directly related to the vascular activity of principally periosteal but also metaphyseal and diaphyseal (nutrient artery) vessels (*12*).

Autoradiographic studies show that Tc-99m-labeled pyrophosphate is found diffusely distributed in the mineralizing tissue of areas that have a high rate of new-bone formation. In rats, maximum uptake in 1-week-old fractures is seen surrounding both bone fragments, and an area of minimal activity is left just around the fracture line. At 2 weeks, uptake is intense around the entire fracture area, and it then decreases gradually within the next 8 weeks (*13*). There is no uptake in the procallus or in the fibrous and cartilaginous tissues.

Gumerman and associates describe an uptake pattern that is probably based on increased uptake by areas of new-bone formation, first peripherally to the fracture line (biphasic) and later including the fibrocartilaginous callus (one peak). The pattern described resembles that found in normal bone-graft healing (*8*). Since the orderly progression of ossification is inhibited in delayed union or nonunion, abnormal uptake patterns result, as shown by the authors. Undoubtedly, local hyperemia also affects the uptake pattern. But in general, ossification, hyperemia, and neovascularization are closely related.

It may be possible in the future to follow fracture healing in humans with one or two Tc-99m-labeled pyrophosphate scans carefully spaced. At present the method appears to be practical and economical in fracture studies using the rabbit model.

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