The Biology of Fracture Healing

An Overview for Clinicians. Part II

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Bone healing problems can be divided into: technical failures, when treatment problems have impaired normal biologic potential; biologic failures, when biologic malfunctions have made the correct treatment ineffective; and combinations of the two. Biologic failures include inadequate callus formation or lack of a normal regional acceleratory phenomenon (RAP), normal modeling or remodeling, or maldifferentiation of the healing tissues, plus combinations. The most common biologic failures involve the inability to form callus and/or a normal RAP. When an inadequate RAP combines with inadequate callus production, then chronic infection, nonunion, multiple failed bone grafts and fixation procedures, and even amputation can ensue. Accumulating evidence suggests that most biologic failures stem from problems attributable to mitogens, differentiating and priming agents, growth factors, and other labile biochemical and biophysical messengers and signals in the region of the fracture itself. The ability of bone to heal can differ in different parts of the bony skeleton at a given moment. Until the basic causes of such problems can be corrected, present-day clinicians must manage them by presently available treatments while conducting research that might resolve them. The causes of most biologic failures probably act within the first weeks after the fracture, although it may take months for clinical roentgenograms to show their effects.

The material in Part I, when combined with clinical, roentgenographic, and pathologic evidence, suggests an etiologic classification of healing problems. Subsequent sections will discuss treatment and research addressed to both.

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A CLASSIFICATION OF BONE HEALING PROBLEMS

Some classifications of nonunions have focused on the roentgenographic appearance (*e.g.*, hypertrophic and atrophic nonunions[17,69]), while others have focused on biomechanical aspects of bone healing[80,81] or on its biology at the cellular level.[12,15,24]

In 1973, three general groups according to their apparent major causes were suggested: technical failures, biologic failures, and combinations of the two.[27,28] Knowing their causes injects a certain rationale into treatment decisions, a rationale supplemented by what empiric experience teaches.

TECHNICAL FAILURES

In this situation, the biological processes had normal potentials, but treatment problems kept them from functioning properly. These problems include infection, poor reduction, distraction, repeated gross motion of the fracture fragments, especially pistoning and shear, and loss of local blood supply due to the injury and/or surgical procedures (Figs. 1 and 2). Their consideration lies outside the purview of this report because many

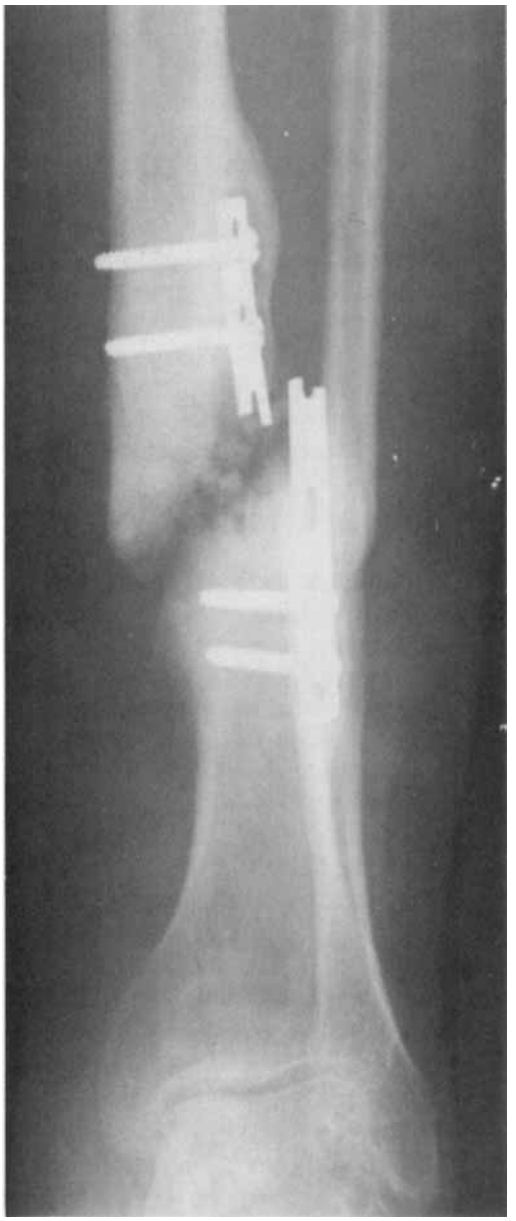


FIG. 1. A technical failure. Abundant amounts of callus on either side of this tibial pseudarthrosis four months after the original injury prove the competence of the biologic activities and mediator mechanisms that make fracture callus. A postoperative wound infection plus the use of a short rather than a long leg cast postoperatively defeated the local biologic processes by fracturing the plate in fatigue and adding increased motion of the fragments to the local infection. Union followed three months after removing the hardware, debriding the pseudarthrosis, and using antibiotics and an external fixator to maintain adequate reduction and fixation.

articles, reviews, symposia, and texts have discussed them since 1977. In the author's experience, technical problems cause or contribute to about 70%–80% of all delayed unions and nonunions of fractures, bone grafting operations, osteotomies, and arthrodeses in the United States and Canada. They affect cortical bone more often than spongy bone. Roentgenograms of a technical failure of a long-bone fracture show adequate amounts of callus on the ends of each major fragment separated by a pseudarthrosis of some kind (Figs. 1 and 2). For that reason, they have also been called hypertrophic nonunions. These failures seldom need bone grafting to promote healing. Eliminating excessive motion and infection and improving reduction usually leads to union. An exception is the synovial nonunion, which requires resection of the cartilage-covered ends of the nonunion because of a special tissue "gating-barrier" effect described elsewhere that can prevent ossification across cartilage layers separated by synovial fluid.[17,28,50] Technical failures formed a major problem in fracture treatment before 1935 to 1940, but antibiotics and advances in surgical and fixation techniques have resolved most of them, leaving as a major problem today another group of failures. Before 1935–1940, these failures comprised so small a fraction of all healing problems that they were considered rarities.

BIOLOGIC FAILURES

In this situation, abnormalities in the biology of the healing processes delay or prevent union even with proper treatment. These failures have recognizable subgroups that, in the author's experience, can each occur independently of as well as accompanied by

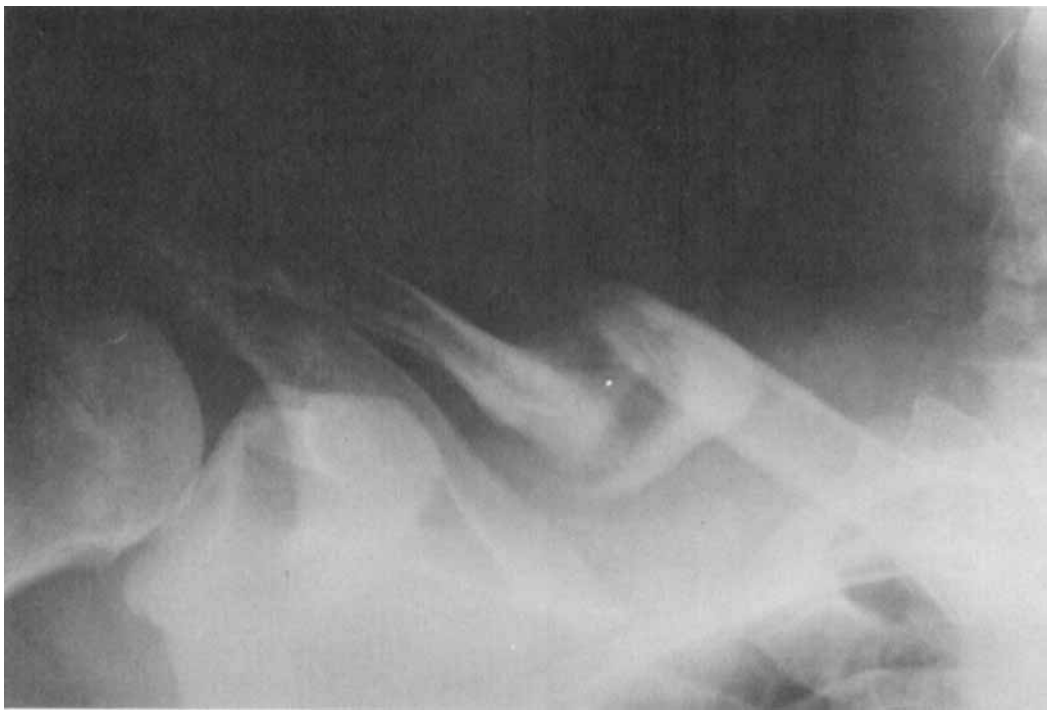
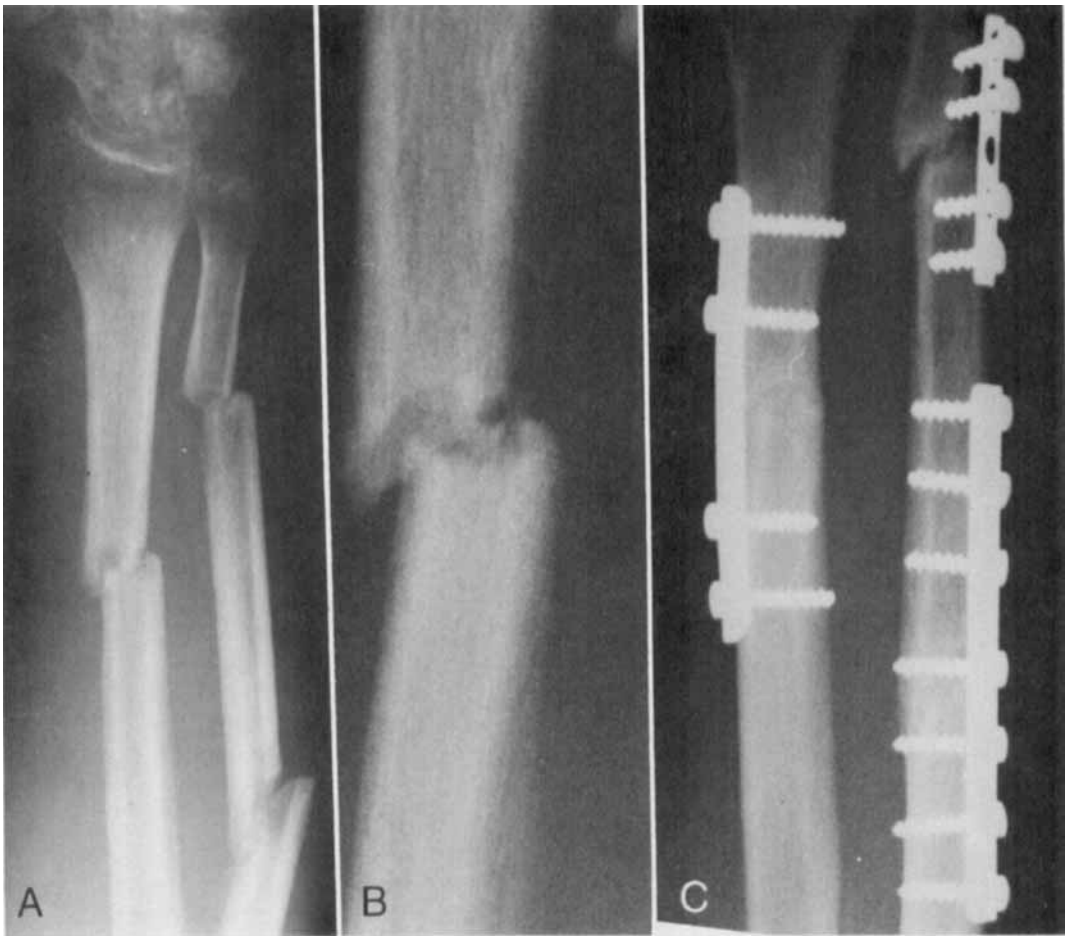


FIG. 2. A pseudarthrosis of an adult motorcyclist's clavicle fracture five months after injury. Abundant callus proves the competence of the local mediator mechanisms that lead to and produce callus. This situation was caused by noncompliance of the patient due to a head injury.

any other. They probably account for about 20% of all nonunions in the United States and, in combination with technical problems, contribute to another 20%. They occur mostly in cortical bone and seldom in spongy bone. Some delayed unions or nonunions combine two or more of the following biologic impairments, and one combination is especially difficult.

Failure to Make Callus. When callus appears in inadequate amounts or not at all in a long-bone fracture, the mediator mechanism(s) that should produce it has malfunctioned. That impugns as a cause the poorly understood initial sensitization–stimulation–proliferation–differentiation–organization of callus formation described in Part I of this work.[33] Such a malfunction occurs in about 80% of all biologic failures in the United States and Canada. Roentgenograms that fail to show adequate amounts of callus two or more months after a long-bone fracture reveal that the local biology cannot produce it, or that a systemic metabolic abnormality prevents chondral and bone matrices from mineralizing so a roentgenogram does not show them, or both. Defective mineralization of callus seldom occurs in the United States today (discussed below) so local biological processes cause most such problems (Fig. 3). Histologically, some of these failures produce little new tissue of any kind in the fracture space while others produce abundant amounts of fibrous tissue (discussed below). Therapeutic X-radiation and some cytotoxins used by oncologists can cause these malfunctions, as can regional denervation and possibly some nonsteroidal antiinflammatory agents.

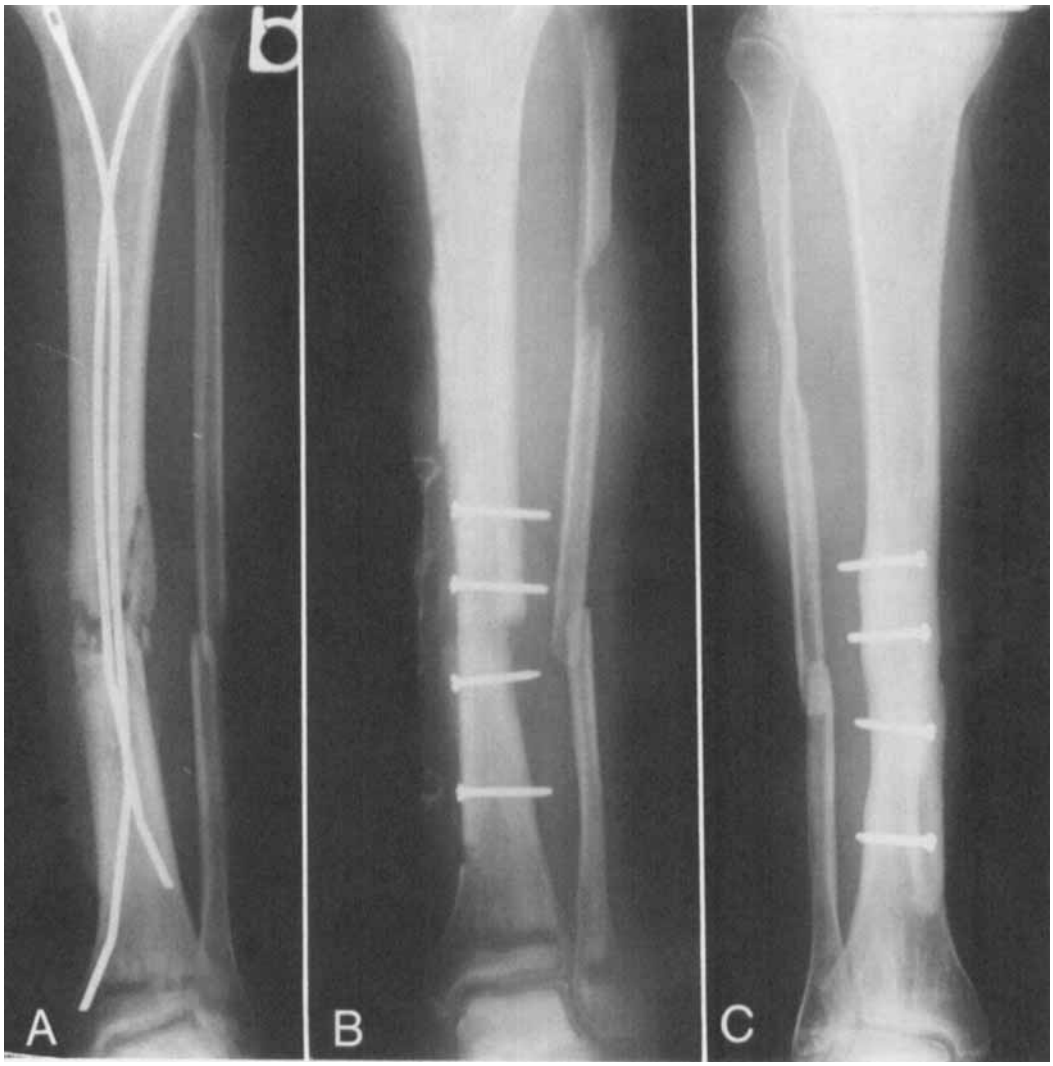
Inadequate Regional Acceleratory Phenomenon. An inadequate regional acceleratory phenomenon (RAP) can lead to slow



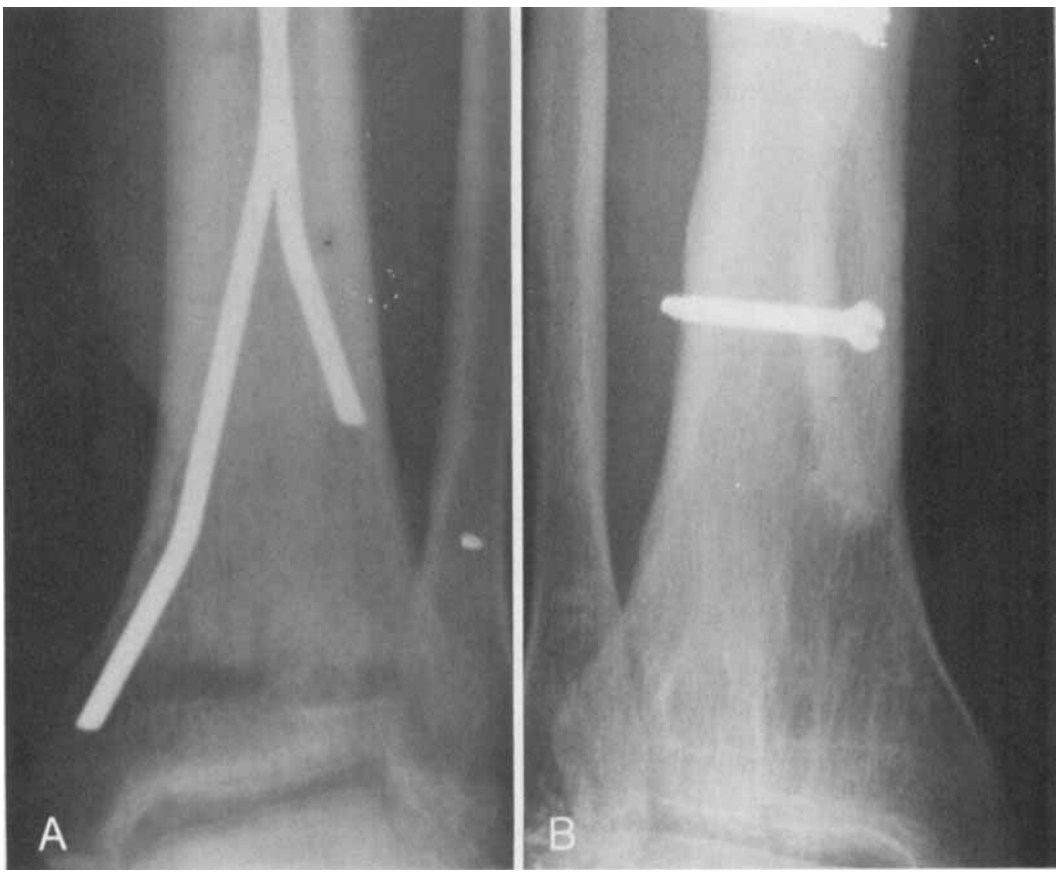
FIGS. 3A–3C. (A) Three forearm fractures in a healthy male in his late 20s. Five months after treatment, these three forearm fractures in a long-arm cast show no visible callus. The metaphyseal and carpal bone osteopenia show that good RAP occurred in the radial metaphysis (compare this to Fig. 7). (B) This magnified view shows cortical tunneling due to greatly increased haversian envelope remodeling, in turn due to disuse plus a good RAP. (C) Four months after compression plating without bone grafting, the remodeling process united the radius and the proximal ulnar fracture. The screws pulled out of the distal ulnar fracture, resulting in increased motion and preventing union. The patient resumed working at this time and is still working seven years later. Note that, many years after the original injury, the distal ulnar fracture remains ununited but asymptomatic. The original osteopenia of the shafts and radial metaphysis resolved within nine months after the patient returned to work.

callus formation and its replacement by lamellar bone. Inadequate RAP probably occurs in less than 3% of all long-bone fractures. However, it contributes to about 75% of the biologic delayed unions and nonunions the author has seen in the United States and Canada and happens more often in cortical than spongy bone.

Figures 4 and 5 show that the shaft of a fractured major bone such as the tibia can have an inadequate RAP while its metaphysis can have an excellent one. Three or more months after injury, clinical roentgenograms provide a clue to an absent RAP: There is absent or minimal longitudinal tunneling of the local compacta and/or trabecu-



FIGS. 4A–4C. (A) A 26-year-old man sustained a complex injury to the leg in a motorcycle accident five months before this roentgenogram was taken. Treatment had consisted of internal fixation, a skin graft, and a long leg cast. The wound was draining small amounts of seropurulent material through a small sinus, but the patient had no fever, inguinal lymphadenopathy, or regional cellulitis. He had been advised to consider a below-the-knee amputation. Note the excellent metaphyseal osteopenia due to a local RAP, but no such evidence in the tibial diaphysis or the fibula. An RAP can develop in one part of a major bone but not in another part of the same bone. Also note no visible callus at either fracture. (B) Three months after removal of the hardware, sequestrectomy, and long leg casting, the wound healed without drainage, and a securely fixed and well-fitted sliding bone graft was done. Part of the proximal fibula was resected to allow good contact and alignment of the tibial fragments. (C) Two and one-half years later, the fracture had a solid union, which took 12 months to develop, and the patient had no infection, drainage, or pain.



FIGS. 5A–5D. The same patient as in Figure 4. (A) Evidence of the tibial metaphyseal osteopenia and RAP five months after injury. (B) The missing metaphyseal bone has mostly returned two years after successful bone grafting and the patient's return to work. (C) There is no evidence of cortical tunneling or RAP in the shafts of the bones five months after injury. (D) A solid tibial union has occurred two years after the successful sliding bone graft. However, the fibular fracture remains unhealed and still without visible evidence of any callus formation.

lar osteopenia in adjacent metaphyses. When the longitudinal tunneling and the metaphyseal osteopenia are present, they stem from greatly increased local basic multicellular unit (BMU)-based remodeling and an associated increase in the remodeling space. Both acute mechanical disuse and the RAP can cause these increases, and their effects combine in normally healing fractures. Another clue to a poor or absent RAP is a cold or cool regional scintigram.[19,20,53,67] The increased uptake of technetium shown by bone scans in the major fragments of normally healing fractures comes from greatly increased regional bone formation,[9,28] in turn due to increased BMU-based remodeling or bone turnover, due in its turn to the combined effects of a RAP plus mechanical disuse.[28,72] Therefore, cold bone adjacent to a fracture callus two or more months after a fracture means an inadequate or absent RAP, which usually means healing will be slow.

An adequate RAP need not mean adequate callus formation (Fig. 3). Callus for-

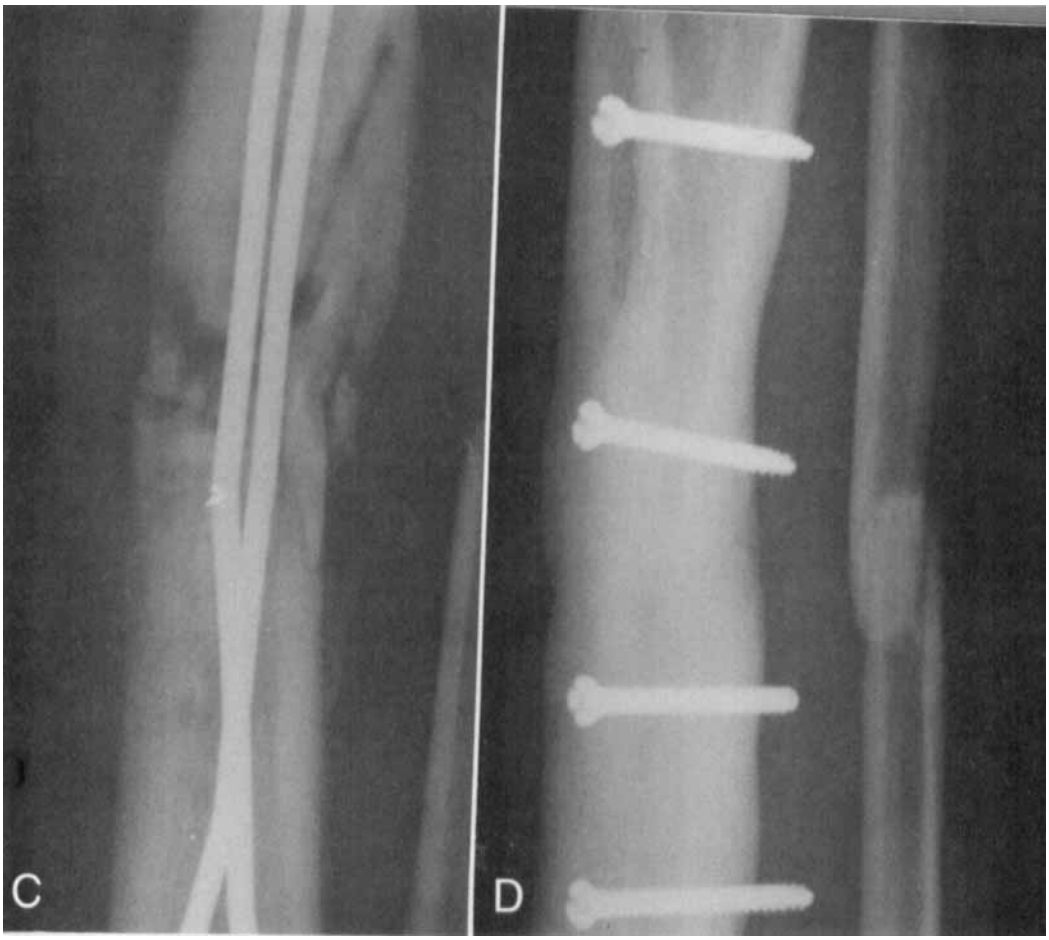


FIG. 5 (*Continued*).

mation and the RAP can malfunction separately.

Some medical problems accompany inadequate RAP often enough to suggest a cause and effect relationship, but the mechanism is still unknown. The associated medical problems seen by the author include (in part) diabetes mellitus (the lower extremities of such patients seem especially prone to inadequate RAP); peripheral neuropathies of any origin; major regional sensory denervation due to other causes including syrinx, tabes, and peripheral nerve transection; diphosphonate intoxication; severe radiation damage; and severe malnutrition. However, more than 70% of clinically observed impaired RAP had causes unknown to the author. Since 1966, numerous efforts have failed to identify possible systemic causes from medical histories, examinations, consultants, and clinical laboratory tests of blood and urine. Of interest, inadequate RAP seldom occurs in children, in healthy laboratory animals, and, to repeat, in spongy bone (but see below).[28]

Failure to Mineralize Callus. This can occur in most kinds of osteomalacia (but, curiously, seldom in vitamin D-resistant rickets[3,28,68,77]), thereby leading to pseudofractures and to nonunions of traumatic

fractures, surgical osteotomies, bone grafting operations, and arthrodeses.[22,23] Correcting the systemic metabolic abnormality usually lets the callus mineralize, whereupon subsequent healing tends to proceed normally. That the subsequent modeling and BMU-based remodeling stages apparently cannot occur until the callus mineralizes suggests to some that the mineral plays a role in enabling those processes.

These failures seldom arise; they seem to cause or contribute to less than 3% of all delayed unions and nonunions in the United States.

Maldifferentiation. If the initial tissue reactions of sensitization–stimulus–proliferation occur properly but produce fibroblasts and/or lipoblasts instead of chondroblasts and/or osteoblasts, the fracture space fills with scar tissue and fat instead of callus. Some metastatic tumors[2,6,8,40] and treatment problems can cause such failures (especially distraction), but in the experience of the author and others,[1,37,47,52] biologic malfunctions of enigmatic origin account for some of them. Unusual causes include chronic primary hyperparathyroidism,[28] neurofibromatosis,[68] diabetic neuropathy, total local denervation,[14,28] and congenital pseudoarthrosis of the tibia.[68] Healing failures due to maldifferentiation seldom occur in the United States and Canada, where they probably cause or contribute to less than 10% of all biologic delayed unions and nonunions. As an aside, however, they probably occur in more than 50% of technical failures.

Remodeling Stage Malfunctions. Enigmatic malfunctions of the BMU-based remodeling mechanism can delay replacement of apparently normal callus by lamellar bone.[28] Callus does not provide a mechanically durable structural material, for, unless it is replaced by lamellar bone, it breaks down with mechanical usage. As a result, early healing proceeds normally in kind and rate in these cases, but, soon after function resumes, the callus becomes plastic, and deformity begins to develop. This problem is rare since the author has seen or recognized only seven cases in more than 40 years, and others have not yet recognized it or described its pathogenesis. It has led to malpractice suits. Efforts to find medical, biochemical, or endocrinologic explanations for it have failed. In one child who was treated with double tetracycline bone labeling and rib biopsy in 1966, no histomorphometric abnormalities were recognized.[36,54]

Modeling Stage Malfunctions. These are the rule in children with osteogenesis imperfecta.[28,29,62,64] As one result, the deformities of multiple fractures can persist and accumulate and require surgical correction (Fig. 6).

These patients usually form callus rapidly and replace it normally with lamellar bone. Their modeling defect is usually partial rather than total. Imperfecta children with total or near total inability to replace woven with lamellar bone or to model bone usually die at or shortly after birth from numerous fractures arising during birth or even *in utero*.[2,8,62,64]

Modeling stage malfunctions can also occur in osteomalacia and most kinds of rickets[7,68] to contribute to femoral and tibial bowing, perhaps due to the associated inability to mineralize new circumferential bone lamellae produced by formation drifts, an inability that creates another "gating-barrier" effect that prevents or retards corrective modeling drifts.[28] However, osteomalacia as well as rickets now seldom occur in children in the developed nations.[7]

The ability to model bone usually becomes ineffective after skeletal maturity.[29] While roentgenograms taken years after an adult's fracture has healed usually show some effort to recontour the bone's periosteal and cortical–endosteal surfaces, it never reaches completion. In contrast, the BMU-based remodeling activity continues for life.[42,51,74,76]

Mechanical Influences on Modeling. The major stimulus for corrective modeling of a fracture probably does not come from the fracture itself. It comes from biologic reac-

tions to increased local mechanical strains of the still-flexible healing bone. In that respect, considerable evidence suggests that a kind of optimal "mechanical usage window" exists such that both too little and too much mechanical loading of a healing fracture (and ligament) can have adverse effects, but of different kinds, on healing. Yet a range of mechanical activity lies between these extremes that promotes faster healing. Many investigators have published strongly suggestive experimental evidence for such a phenomenon.[41,74,80] Some predictive and quantifiable processes for how bone modeling and remodeling respond to mechanics were described recently,[31,32] and some biomechanicians have begun to study them. Muscle loads and body weight cause these strains,[18] and an ongoing RAP accelerates modeling responses to them.

In summary, the failure to make callus and an inadequate RAP seem to account for most biologic failures of the overall bone healing process seen in the United States and likely in other developed nations.

SOME PATHOGENETIC MEANINGS

Most bone healing failures stem from problems in the first week or so after a fracture, osteotomy, or bone grafting operation, whether technical failures or biologic ones. Accordingly, when considering bone healing problems or experiments, clinicians and investigators should ask not what is wrong with the osteoblasts, but what went wrong with the processes that form them.

Bone healing depends on interactions between circulating systemic factors and other local factors in the fracture, bone grafting, or arthrodesis region, including the bone and adjacent soft tissues.[10,15,24,28,36]

Systemic factors can include hormones, drugs, age, gender, species, nutrition, and unknown factors. They tend to act continuously, for long time periods, and in the whole skeleton. Local factors are of at least two kinds. One consists of the biologic competence of the local tissues at the time of injury, meaning their ability to perceive and respond to both local and systemic messengers that enable and guide healing. Clinical evidence strongly suggests the biologic competence can vary in different parts of a given skeleton at any one time and probably for more than one reason. For example, an auto

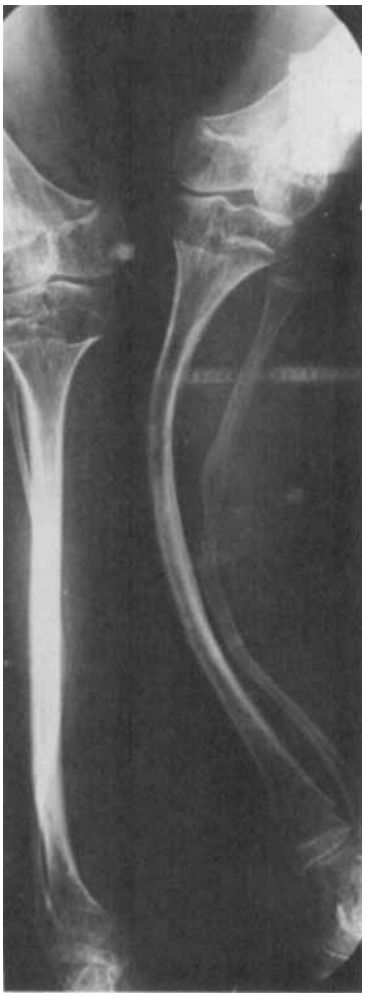
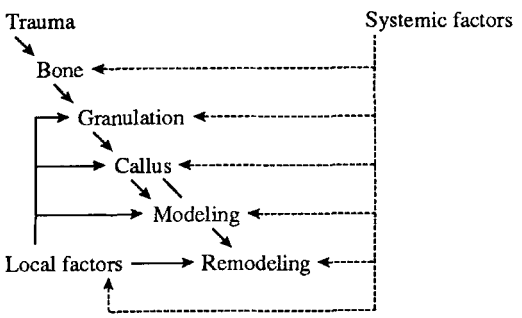


FIG. 6. A patient with osteogenesis imperfecta has had multiple tibial fractures leading to cumulative deformity that his congenitally impaired modeling mechanism could not correct. The tibia on the right has already been successfully treated surgically. A similar procedure will be performed on the tibia on the left.

accident victim with ten fractures can heal nine normally but develop a biologic failure in the tenth, a not unusual situation.[4,11,15,28,35,37,52,66,74] Biologic failures tend strongly to affect cortical rather than spongy bone. For example, a diabetic patient with excellent pedal pulses may fail to heal properly from an injury or infection to a toe or foot but seldom has similar problems in the hand. Healing problems in denervated or heavily irradiated parts of the body have been known to surgeons for decades (see below). The second kind of local factor comprises the biochemical and physical messengers initially liberated by the injured tissues and others provided at the completion of each stage in the healing sequences.

These local messengers tend to have short half-lives, on the order of seconds to minutes, and occur in very small quantities.[51,55,56,75] Because local cells and intercellular materials create and/or release these messengers, their action is confined to cells near them with little spillover into the general circulation. Although this mechanism tends to confine the healing processes to the region of an injury, it is hard to measure these messengers in a patient's blood. This may partly explain why so little is known about them. This idea can be expressed as:



COMMENTS ON TREATMENT

The Technical Failures

That the biologic processes function properly as shown by adequate callus on either side of a pseudarthrosis means that correcting the treatment problem will usually lead to satisfactory union. The author suspects that most successes of the electrical treatment of fractures fall into this group.[17,33,46,71,79]

The Biologic Failures

Rarities before 1935–1940, these failures now provide the major challenge facing clinicians and scientists trying to facilitate human bone healing. Most failures of the electrical treatment of fractures or bone grafting procedures belong in this group. Comments on particular types of problems follow. Note at the outset that impaired preexisting circulation causes few of them. However, an impaired ability to create the new local capillary networks needed for good healing after injury may well participate in some of them, particularly in diabetes. Angiogenesis is essential to all soft- and hard-tissue healing, as experimental pathologists have proposed since 1920, but its exact role in the kinds of problems discussed here remains obscure.

Inadequate Callus. When inadequate callus causes a delayed union or nonunion, one should realize that any subsequent treatment that depends on making callus will tend to fail (but see below). That includes unfixed onlay and inlay grafts, whether autogeneic or not, and unfixed closed reductions. When agents that alone or in combination (cytokines such as bone morphogenetic protein or other mitogens, growth factors, and differentiating agents) can evoke callus formation reliably, this problem will probably resolve.[10,49,55,75] Fresh autogeneic cancellous bone may excel as a graft material in these problems because of the varied labile biologic messengers it delivers to the tissues and mediator mechanisms in the recipient site.

Since the BMU-based remodeling process often proceeds normally in these cases (but not always; see below), intimate and rigidly fixed contact of the fracture surface will let remodeling unite the fracture with osteonal rods crossing it.[53,57–61,65,67] Suitable surgical

techniques include internally fixed sliding grafts (Fig. 4), plates (Fig. 3), and intramedullary devices.

In these situations, unfixed grafts tend to fail because their success depends on embedding and incorporating both the graft and its host bone in a common callus that cannot form properly in these cases (but see below). Nonautogeneic bank bone of any kind can add to that problem an impairment of the recipient site's mediator functions by the host's immunologic reaction to foreign proteins in the graft.[12,15,24,36]

While the author has called healing by BMU-based remodeling the secondary healing process because it follows the initial callus phase,[28] other authors have called it part of the primary healing process,[57-61] a statement that does not invite debate; it simply explains. The remodeling process usually needs five to eight months to provide good union, but given the basic requirements of contact, fixation, and time, it is usually reliable.

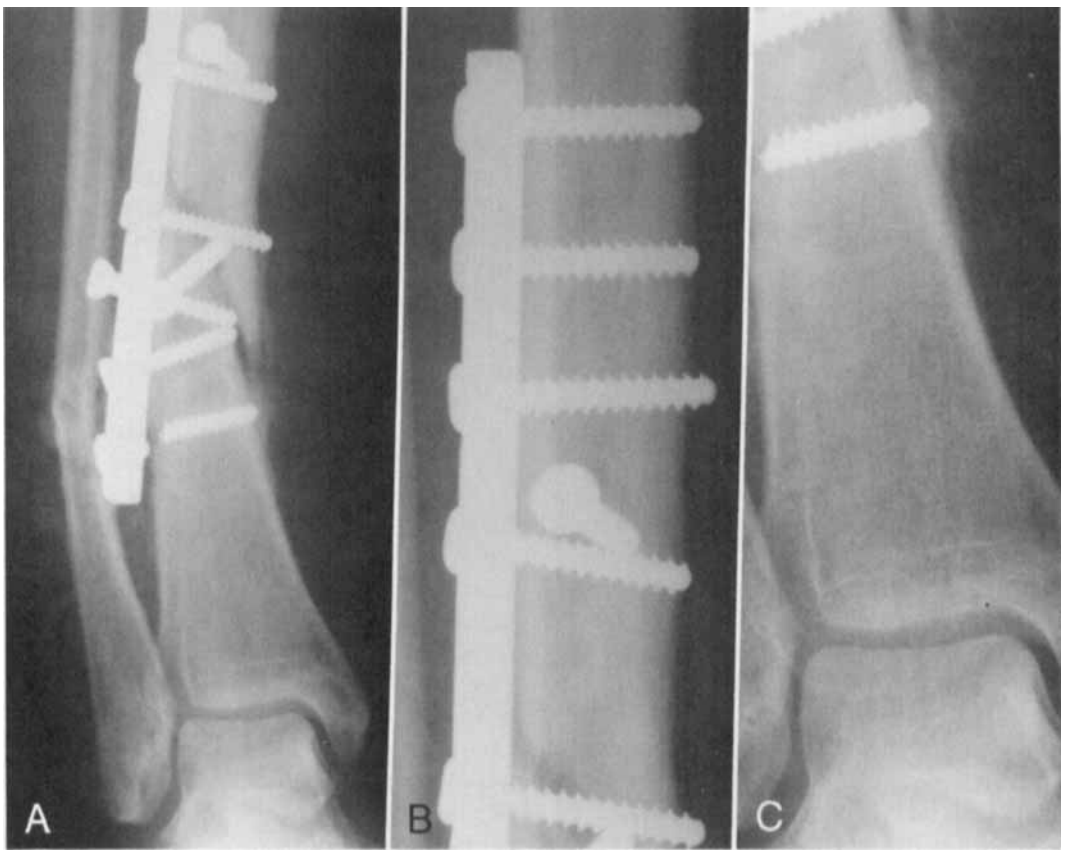
Some clinicians blame these failures on poor local blood supply, but this is probably incorrect for at least three reasons. First, if the blood supply were poor, such healing failures would have cold scintigrams, but they usually have warm or hot ones that prove increased bone perfusion.[17,20] Second, they would also have low oxygen tensions and reduced local histologic activities, but they usually do not.[9,13,15,24,34,40,45] Third, if local blood supply were poor, then a grafting and/or internal fixation operation would only make it worse because the surgical exposure reduces any preexisting blood supply, which should impair bone healing even more afterward.

There is an important difference between poor blood supply due to impaired perfusion before the moment of fracture because of atherosclerosis, for example, and the quite different matter of an inability to create the new capillaries and associated vessels always needed for normal healing after the moment of the fracture. The latter problem can be seen in the lower extremities of diabetics, in regions that have received large doses of therapeutic X-radiation, or in the situation described immediately below.

Inadequate RAP. Here, healing proceeds slowly but ultimately in adequate amounts and in a normal sequence, so former teachers (Colonna, Bosworth, Boehler, Codman, Phemister, Watson-Jones, and Miyazaki) advised that prolonging immobilization of a fracture or arthrodesis usually led to union. Electrical treatment may often facilitate RAP,[69-71] and the trauma of an open bone grafting and internal fixation operation usually creates its own new RAP that improves subsequent healing.[28] Successes of the former practice of drilling slowly healing fractures may stem partly from the new RAP it causes. Enhancing RAP with biochemical agents is an attractive but little explored idea, partly because little is known about RAP and its roles. In that regard, both High[38] and Shih and Norrdin[63] have now shown that PGE_2 (a prostaglandin) does seem to facilitate RAP in the repair of experimental fractures and other bone trauma in dogs.

Impaired Remodeling Stage. Here, prolonging immobilization by two to four times can facilitate remodeling. However, bone grafts in two such children subsequently completely resorbed, along with significant amounts of the ends of the fracture fragments. The impairment of bone healing in these children even though soft-tissue healing was normal strongly suggests its cause lies in the local bone biology and mediator mechanisms rather than in a systemic abnormality that affected all bones and soft tissues.

Inadequate Callus Plus Inadequate RAP. This fortunately infrequent combination can have serious consequences. Such a fracture may take longer than a year to heal if rigidly fixed and accurately reduced. It seldom heals otherwise. Such patients also tend to develop delayed wound healing, wound disruption, chronic indolent ulcers, and chronic but superficial wound and local bone infections, particularly in the leg and forearm. The au-



FIGS. 7A–7C. (A) A 30-year-old patient sustained this fracture five months before this roentgenogram was taken. During that time, three weeks of initial closed treatment in a cast was followed by the open reduction and internal fixation shown here, which initially was anatomic. The tibial fractures were barely visible on postoperative roentgenograms. But the incision did not heal, and the patient developed a chronic wound ulcer and was treated with antibiotics (though no clinical fever, lymphangitis, adenopathy, or cellulitis was noted) and three skin grafts in the next four months by two different plastic surgeons. All of these treatments failed. Three months after injury, the fracture was judged to be healed and weight bearing began, whereupon the loss of reduction and fixation shown here followed within a week. (B) There was no visible callus or intracortical tunneling at the time of this roentgenogram. (C) No metaphyseal osteopenia appeared even after five months of mechanical disuse, so no RAP appeared in either place. Compare this figure to Figures 3, 4, and 5. A small wound sinus drained small amounts of serosanguinous fluid, but not pus, which one 2 × 2 dressing sponge easily absorbed daily. There was no fever, local edema, lymphangitis, cellulitis, or inguinal adenopathy. The patient was healthy but significantly overweight.

thor believes greatly retarded local angiogenesis is a significant factor (Fig. 7). Treatment of such patients could include perioperative antibiotic coverage with any operative procedures, ten to 20 days of postoperative bed rest with elevation of the limb to minimize edema, accurate reduction and rigid fixation of fragments and any grafts, and prolonged postoperative deloading of the injured bone to avoid fatigue of bone at bone–implant interfaces that would lead to loss of rigid fixation. Under these conditions, a satisfactory union could be expected in six to 14 months.

At present, there is no way to predict at the

time of an original injury, arthrodesis, or osteotomy which patient will develop any of the above problems, except for the diabetic and neurologic factors discussed earlier. Possibly, improvements in the rapidly developing nuclear magnetic resonance technology may permit the earlier detection of such problems in the future.

The Second Injury Phenomenon. Although controversial, this phenomenon may be real. If 100 cases of a particular fracture, *i.e.*, a femur or tibia, are promptly internally fixed and are compared with 100 cases of the same fracture fixed ten to 40 days after injury, fewer than one-half as many healing failures occur in the latter than in the former group. While most experienced clinicians have seen this phenomenon,[16] studying it has challenged and confused experimentalists. Partly this is due to a tendency to equate rates and abundance of healing in such groups with their ultimate success/failure ratios, and partly it is due to the fact that the animal models usually used to study the phenomenon rarely develop biologic failures of bone healing. In fact, probably fewer than one of 50 fractures in such animals will show evidence of a biologic impairment. As a result, investigators compared the already good healing potential of original fractures in, for example, five to 20 control animals to the equally good healing in five to 20 experimental animals. In contrast, Urist and McLean[76] showed experimentally in 1950 that multiple fractures and refractures do not seem to impair bone healing, in agreement with human clinical experience.

Improved healing after a second injury becomes clearly apparent only when two conditions are met. First, a biologic failure would have followed the first injury had a second injury not happened. Second, the second injury should occur more than a few days but less than two to three months after the first one. The biologic basis for the second injury phenomenon and the exact time window within which it is most likely to occur both remain obscure.

An On–Off Phenomenon? Bone grafting and internal fixation procedures of some biologic failures done many months or more than a year after the original fracture have led to prompt and occasionally even exuberant subsequent healing.[11,35,37,52,74] Comparing roentgenograms of the preoperative failure to the final postoperative success leaves little doubt; a great change happened in how the bone responded to injury between the two events. While the surgeon may receive all the credit for such effects, probably much of it should go to biologic processes instead.

These observations suggested an idea proposed in 1986.[28] Some biologic failures may reflect an only temporary and local inability to heal normally, a kind of off state of the local mediator mechanisms. An injury may occur during such a stage, but a subsequently successful operation may be done after that inability has resolved, and so during an on state. Such off–on states do occur in bone physiology. While controversial when first proposed in 1960–1964,[25] Hori *et al.* proved their occurrence in 1985 in elegant tissue time-marking experiments.[39] To date, only people concerned with metabolic bone diseases know about and have studied this idea.[48,54] Earlier, clinical situations were discussed in which those mediator mechanisms were clearly off in one part of the body but on in other parts at the same time. Further discussion of this idea appears in other reports.[28,30] It merits emphasis that these phenomena appear more often in human clinical experience than in animal experiments or veterinary clinical practice.

COMMENTS ON RESEARCH

That the molecular–biologic causes of biologic failures of bone healing remain obscure suggests five points: (1) The new bone biology that has evolved in the past two decades suggests that research should refocus from osteoblasts toward the mediator mechanisms that form them.[21,28,30,41–43,51,55,75,79] (2) The research should focus on the local as well as systemic factors that control the mediator mechanisms. (3) It should focus on the early

phases and early parts of each stage of the healing process rather than the later ones. (4) It should focus on how a given agent affects each stage of the healing process rather than on its final overall effects. (5) It should focus on how and why each mediator mechanism responds to challenge. After all, a healed fracture represents successful and partly sequential responses of many such mediators to the challenge of the original injury.

Technical Failures

Many adult mammals can provide good model systems of these failures for study by experimentalists, implant manufacturers, and drug houses. Growing animals probably provide poor models for such studies because of their normally superior healing potential. There is no convincing evidence that any known treatment materially improves it.

Biologic Failures

To date, no animal models are known to provide impaired RAPs, biologically impaired callus production, impaired tissue organization, or maldifferentiation. Since collectively these problems cause most human biologic failures, efforts must be made to find or create such models.

Some drugs or treatments react differently during bone healing in healthy animals and in human biologic failures.

Most human bone healing problems affect cortical bone rather than spongiosa, which heals well except when associated with local infection, marked distraction, or intrusion of joint fluid into the fracture, and even in very ill or malnourished subjects. Studies of healing mechanisms would be most productive if done in cortical bone. Even there, small defects such as drill holes one-quarter of the outside bone diameter usually heal well, again especially in growing subjects. A more severe challenge to the mechanism of cortical bone healing would be large cortical bone defects or established delayed unions/nonunions in older subjects.[10,49,50]

Cell, tissue, and organ culture systems have been used to study the properties and responses of isolated and differentiated cells and have been widely used for studying osteoblasts. However, these methods have basic limitations: (1) Special mediator mechanisms create osteoblasts in the living body and determine if, when, where, how many, and how long this process occurs.[28] (2) These mechanisms and their game rules differ from those of already differentiated osteoblasts.[30] (3) Mediator mechanism problems underlie most bone healing problems that do not stem from poor treatment. (4) However, intact mediator mechanisms no longer exist in present cell, tissue, and organ culture systems. These systems remove the normal circulation, vessels, and neural mechanisms and disrupt the communication between cells and adjacent tissues. (5) As a result, at present, intact mediator mechanisms can be studied only in intact animals.

This suggests that future research will depend on collaboration between people who work with *in vitro* systems and others, such as pathologists and clinicians, who study tissue-domain phenomena in intact subjects.

The Coherence Treatment Concept

It was proposed in 1979 and has since been shown for bone physiology and pathology that novel and beneficial effects can follow properly timed brief and intermittent and/or brief and sequential use of one or more drugs[28] or other agents, including electrical treatment and active or passive motion.[75,79] Continuous treatment with some drugs or other agents can impair a biologic activity that properly timed and brief treatment with the same drug or agent can enhance.[5,28] New and older agents used in such modes will ultimately provide nonoperative solutions to many problems discussed in this work. But first more must be learned about the mediator mechanisms affected by such agents. This type of treatment, *i.e.*, coherence treatment of osteoporosis, has shown some success. The future could see effective treatments for bone healing problems that depend on pre-

cise timing of the delivery and withdrawal of drugs and on better understanding of the biologic mechanisms, events, and sequences that drugs and other agents can influence.

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