# The Biology of Fracture Healing

## An Overview for Clinicians. Part I

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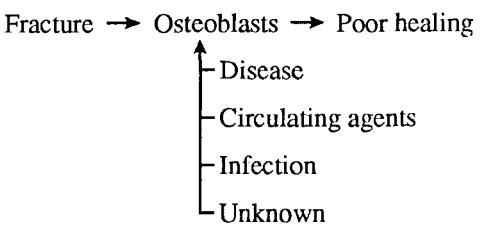
**The bone healing process normally unites fractures, arthrodeses, osteotomies, and bone grafting operations. The process normally proceeds in successive stages named the fracture, granulation, and modeling/remodeling stages. A separate regional acceleratory phenomenon speeds up each of the other stages. The osteoclast and osteoblast cells that make intercellular substances of each stage do not exist in sufficient numbers to heal the bone at the moment of fracture or operation. They are made by local multicellular mediator mechanisms that contain precursor and supporting cells, capillaries, lymph, and innervation, plus local autocrine and paracrine regulation. Under the influences of local and systemic agents, these mediator mechanisms determine whether new local osteoclasts and osteoblasts will appear, in addition to when, where, how many, what kind, and for how long. Errors in those functions can then lead to several kinds of retarded or otherwise abnormal bone healing that will be discussed in Part II of this work.**

In two installments, this work outlines the basic bone healing processes, describes some of the more common problems encountered in orthopedic practice in the United States and Canada and some of their biologic causes, and suggests how these insights can help make treatment decisions and design research concerning them. This work synthesizes multidisciplinary evidence for orthopedists who depend on these processes in their practices or study them in laboratories. The synthesis differs from, but supplements some, descriptions by others, many of which, due to poor communication between basic scientists and clinicians,[1,12,25,39,49,73] could not account for an understanding of the biologic processes related to bone that have accumulated since 1970. Table 1 lists clinical conditions that depend on one or more of the bone macrohealing processes. These processes differ from those described by Burr *et al.*,[11] Schaffler,[56] Frost,[25] and others[13,33,34,43] that heal microscopic fatigue damage.

Since 1975, the understanding of fracture healing biology has begun to change. Before 1965, most authorities viewed osteoblasts as the primary instruments of both bone healing and its major problems, whether the problems stemmed from inadequate treatment, disease, local infection, drugs, some combination of these, or something still unknown:




Experimental studies of that time reflected great concern over how existing osteoblasts

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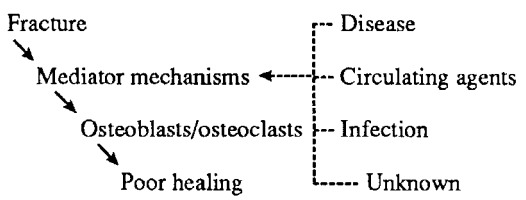
responded to drugs, hormones, systemic disease, mineral ions, nutrition, and other factors.[42,72,75]

It is now known that bone healing requires far more than just osteoblasts.[2,9,10,16,33,37,38,45,52–54] It involves creating and delivering special physical and biochemical signals to cells in special local and multicellular mediator mechanisms in the tissues in the fracture region.[48,55,73] These mechanisms contain their own capillary beds, lymph channels, varied kinds of precursor and supporting cells, intercellular materials, a local communication system, and often, innervation.[17,34,44,76] The local and systemic agents that initiate and subsequently control bone healing do so by acting directly and more frequently on the mediator mechanisms than on any already existing osteoblasts and osteoclasts.[24] In response, these mechanisms determine if and where to make new osteoblasts, osteoclasts, chondroblasts, chondroclasts, and fibroblasts, including how many, when, their activities, how long they will function, and what nourishes them.[24,52,53] One might encode this idea in this relationship:




In addition, it is becoming clear that bone healing failures far more often stem from malfunctions of mediator mechanisms than of already existing osteoblasts or osteoclasts. These mediator mechanisms have a more complex structure, function, and biologic control than was even suspected ten years ago.[48,55,73] Also, since the causes of many delayed unions and nonunions act relatively early in the whole bone healing process, by the time healing problems become clinically apparent, the causes have often passed into history.[24]

TABLE 1. Some Clinical Problems That Depend on the Bone Healing Processes*

| | |
|---|---|
| Fracture nonunions | Ununited surgical osteotomies |
| Delayed fracture healing | Failed surgical arthrodeses |
| Pseudofractures | Refractures |
| Failed bone grafts | Myositis ossificans |
| Heterotopic bone formation | Charcot joints |
| Osteoblastic metastases | Myelofibrosis |

* Collectively, these problems probably affect more than one million people annually in the United States.

Part I of this work describes the sequential biologic activities that normally heal fractures, osteotomies, bone grafts, or arthrodeses. Part II will discuss some of the clinical evidence and meanings.[27]

## THE MAJOR BIOLOGIC PROCESSES IN BONE HEALING

Well before 1960, pathologists knew the basic histology and sequences of five of the six activities described below. Auxhasen[7] described them in 1907, and texts by Albright and Brand,[2] Luck,[39] and Sumner-Smith[65] contain succinct reviews.

The healing process includes the following natural stages: (1) the fracture itself; (2) the production of a temporary soft healing tissue called granulation tissue; (3) the replacement of this tissue by a temporary hard tissue called the callus; (4) the replacement of the callus by well-oriented lamellar bone; and (5) concurrent recontouring of the whole bone toward its normal shape by bone modeling (Fig. 1). An accompanying regional tissue reaction accelerates these processes. Without it, healing takes two to ten times longer. Each of these processes is discussed in detail.

### The Fracture

The fracture injures local marrow, periosteum, and adjacent soft tissues, as well as the living bone itself. As a result, some cells in these tissues die while others are per-

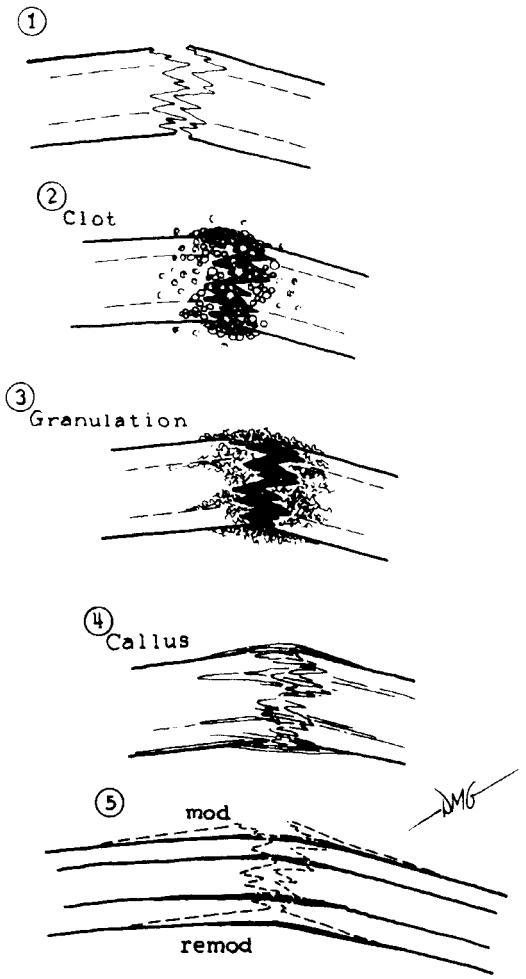
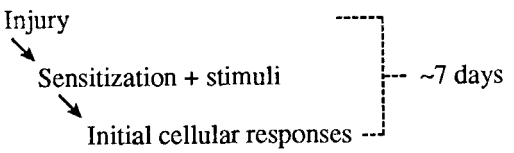



FIG. 1. A long-bone fracture with some angulation showing the separate and sequential stages involved in normal bone healing as it applies to fractures, arthrodeses, osteotomies, and some kinds of bone grafts. The stages progress from initial injury (1) hematoma (2), granulation tissue (3), callus (4), to remodeling and modeling (5). The accompanying RAP is not shown.

turbed.[1,5,35] The injury does two things needed to initiate normal healing. First, by perturbing some of the surviving local cells, it sensitizes them so they can respond better to special local and systemic messengers and stimuli. Second, it releases local and usually labile biochemical and biophysical messengers that make those cells respond and help to determine how they may respond. (Cells respond poorly if not sensitized first.) These messengers include mitogens that make local precursor cells proliferate and messengers that guide the differentiation and organization of the daughter cells.[20,28,45,48,50,54,70] Reviews of such matters by Sachs[55] for hematopoiesis and by Parfitt[48] and Urist *et al.*[73] for bone suggest the future direction of research in the area of bone healing.

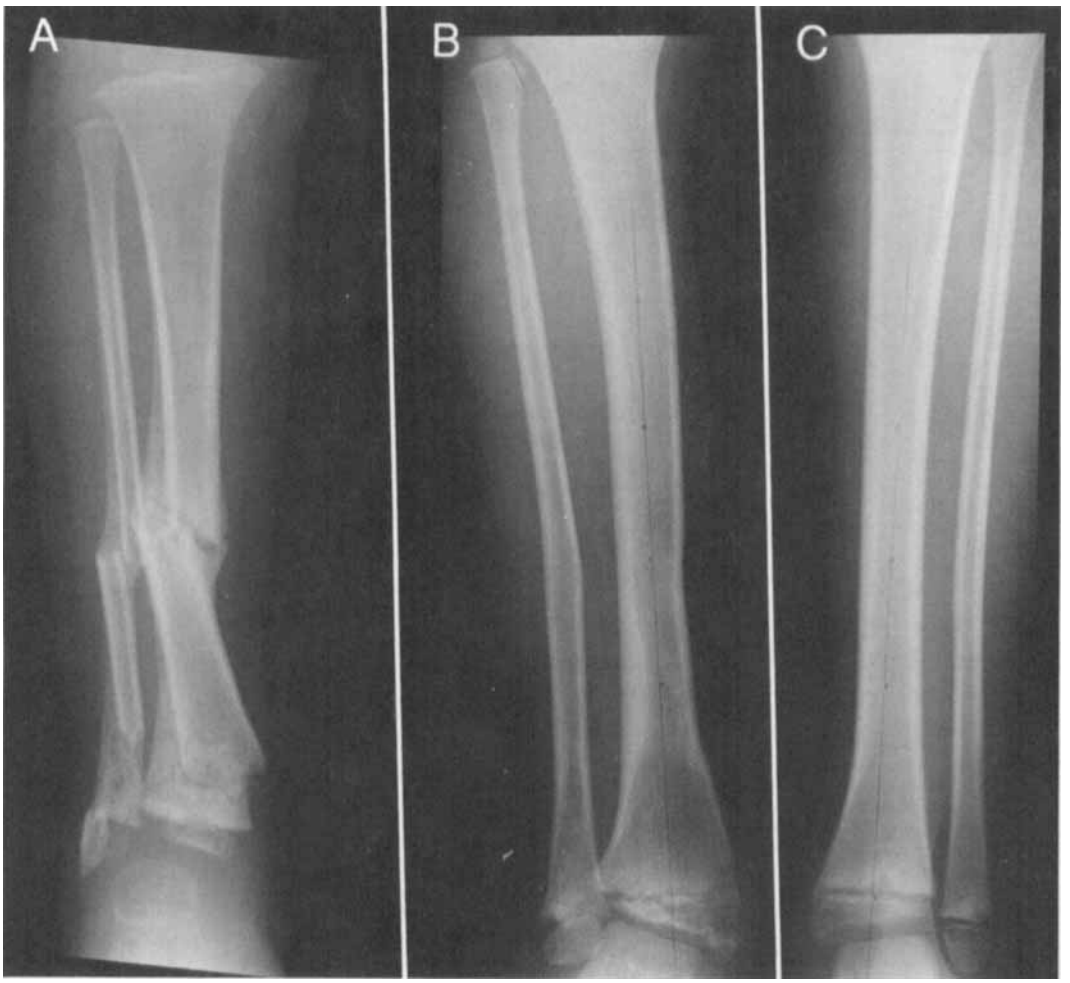
As an aside, each stage of the whole bone healing process depends on many different kinds of differentiated cells to make the new capillaries (including endothelial and smooth muscle cells) studied by Rhinelander,[52,53] the new local connective tissue (including fibroblasts, lipoblasts, and intercellular materials), and the bone and cartilage matrices (made by osteoblasts and chondroblasts). It also depends on poorly understood supporting cells that are always present, including in part mast cells and several kinds of leucocytes. During these processes, the varied local tissue elements also communicate continually with each other.

Essential parts of the first stage biologic responses probably finish within seven days after injury. Yet a clinician may need to wait for months for roentgenograms to show if inadequacies occurred during the original groundwork[24]:




## THE GRANULATION TISSUE STAGE

Precursor cells in the sensitized and stimulated local mediator mechanisms begin to produce new cells that differentiate and organize to provide new vessels, fibroblasts, intercellular materials, supporting cells, and other cells. Collectively they form a soft granulation tissue in the space between the fracture fragments, between a bone graft and its host bone, or between the major fragments of an arthrodesis or osteotomy. When



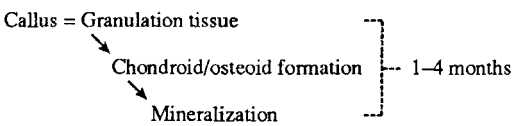

FIGS. 2A–2C. (A) Postfracture modeling in a young patient who sustained complex severe trauma of the leg. (B) The fractures healed satisfactorily, and about two years later, bone modeling drifts had corrected the original zig-zag deformity of the shaft while BMU-based remodeling activity replaced callus with lamellar bone and restored the marrow cavity. (C) The normal leg. (Reproduced by permission, H. M. Frost, Orthopaedic Biomechanics, Springfield, Illinois, Charles C Thomas, 1973.)

a hematoma clot is present (it probably need not be in stress fractures), then macrophages, giant cells, and other wandering cells arise in the granulation tissue to invade and remove it. This stage lasts about two weeks. Some osteoclasts usually appear at this time and erode some of the fracture surfaces. The granulation tissue may be viewed as one of the mediator mechanisms that leads to the next stage.

## THE CALLUS

Further cell proliferation, differentiation, and organization begin to create new chondroblasts and osteoblasts in the granulation tissue. They synthesize the extracellular organic matrices of cartilage and woven bone. A week or so later the newly synthesized matrices begin to mineralize. Mineralization finishes some weeks later with the formation

of the fracture callus, revealed on roentgenograms because of the calcium it contains (Fig. 2). Usually by this time bony union has gained enough strength and rigidity for the patient to resume cautious function. In humans, creation and mineralization of the callus after injury requires from four to more than 16 weeks. Callus formation occurs more slowly in adults and in compact bone than in children and in spongy bone, and its organization usually ignores the orientations of the local mechanical bone strains and loads. The architecture of woven bone trabeculae in callus reflects the orientation of the new capillaries that are created before the trabeculae and that nourish the latter afterward:



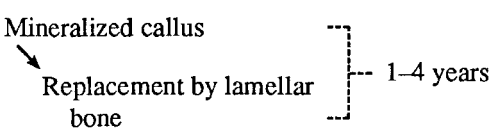

## The Remodeling Stage

Some enigmatic property of mineralized callus makes the packet-style bone remodeling process begin inside it to replace the callus with packets of new bone. The callus probably provides at least one of the mediator mechanisms that marshals the basic-multicellular-unit-based remodeling that will replace it. That remodeling mechanism does four things: (1) It replaces any mineralized cartilage with woven bone to form a kind of primary spongiosa. (2) It replaces the latter plus any other woven bone with packets of new lamellar bone. (3) It replaces callus between the ends of the compacta with new secondary osteons made of lamellar bone that align parallel to the local peak longitudinal compression and tension strains/stresses caused by mechanical usage and muscle forces across the former fracture, osteotomy, or arthrodesis. (4) It also tends to remove any callus plugging the marrow cavity, restoring the cavity (Fig. 2B), in contrast to Wolff's belief.[77] However, Wolff lacked the great advantage of diagnostic roentgenograms. Anderson,[4] Schenk,[57,58] Schenk and Perren,[59] Schenk and Willenberger,[60,61] and others[1,5,9,35,47,50,66] have described those processes.

## The Remodeling Basic Multicellular Unit

The afore-mentioned remodeling basic multicellular unit (BMU) is a particular mediator mechanism that contains many kinds of cells, intercellular materials, and capillaries, all specially organized in space and time and communicating with each other. A BMU first produces osteoclasts that remove a packet of preexisting hard tissue and then produces osteoblasts that replace it with a packet of newly made bone in a stereotyped activation–resorption–formation sequence that consumes three to four months per BMU. Many authorities have reviewed the properties of lamellar bone remodeling BMU since their original description in 1964,[21] but it is still not known why the BMU that removes packets of mineralized cartilage replaces them only with packets of new woven bone, while the BMU that removes packets of mineralized bone of any kind replaces them only with packets of new lamellar bone.

Complete replacement of the callus with functionally competent lamellar bone by remodeling BMU consumes one to four years. It proceeds quickly during the first one-third of the replacement and slows progressively in the last two-thirds (see the regional acceleratory phenomenon below). Failure of the callus to mineralize apparently can block it, as can some drugs (*e.g.*, Didronel, Procter & Gamble, Cincinnati, Ohio):




## The Modeling Stage

About the time callus formation ends, bone resorption and formation modeling

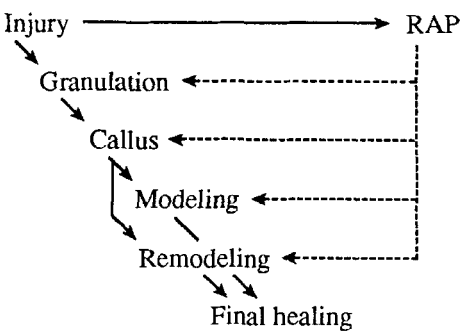
drifts (two further special mediator mechanisms) on the cortical–endosteal and periosteal surfaces of the compacta begin recontouring its gross shape toward normal. That reshaping or sculpturing is called modeling. It can reach completion in young children (Fig. 2B) and nearly so in young adolescents but never in adults.[13,22,24,25,34,71] The process requires one or more years and goes on concurrently with the remodeling processes described earlier. While older literature referred to the sculpturing process as remodeling,[77] it is called modeling today (as in modeling with clay) because it is quite different from the BMU-based remodeling process.[24,33]

Separate but related minimodeling processes on trabeculae inside a bone can realign them to parallel their major local mechanical loads in accordance with recently presented modeling laws.[25] The major stimulus for postfracture modeling activity in both trabeculae and compacta probably comes from local mechanical bone strains caused by muscle forces when resuming physical activity after the callus matures.[14] The regional acceleratory phenomenon described next usually facilitates it.

## The Regional Acceleratory Phenomenon

The essential descriptive pathology and sequential order of the above healing stages have been known for more than 80 years and are outlined in recent basic science and pathology texts. However, the sixth process, the ubiquitous regional acceleratory phenomenon (RAP) was first described as an operational entity in 1983.[23] (Although restricted in distribution, Kolář *et al.*[36] provided descriptions of many of its effects in 1965.) Before 1983, knowledge of this phenomenon spread among histomorphometrists, beginning in 1966 at a special annual bone workshop sponsored by the University of Utah. That acquainted most histomorphometrists with the RAP from 1966 to 1970,[6,13,19,29,30,32,34,40,41,43,46,48,51,67,73] but so far few clinicians know of its existence or roles in clinical problems. Several investigators have studied it recently, including Daum *et al.*,[15] Martin,[41] Shih and Norrdin,[63] Schnitzler and Solomon,[62] and Takahashi *et al.*[68,69]

Somehow, the original injury accelerates these normal regional processes.[24] This acceleration is the RAP. The RAP does not seem to provide new processes, but by increasing the rapidity of the other healing stages, it makes healing occur two to ten times more quickly than otherwise. Since a RAP normally occurs after a fracture, arthrodesis, osteotomy, or bone grafting operation,[23,24] one only appreciates its existence in those few cases (less than 3% of all fractures) in which it does not occur. (Clinicians usually dismiss its roentgenographic bone density effects as due solely to disuse osteoporosis.) It begins within a few days of the fracture, typically peaks at one to two months, and may take six to more than 24 months to subside. The increased intracortical bone remodeling it causes produces tunneling within the cortex that appears on clinical roentgenograms of good contrast and definition (Fig. 3). Its effects are as follows:




## Comments on the Biologic Processes

Several features of the above processes provide background for Part II of this work, which describes how the above material could help to classify and choose treatments for healing problems and to study them experimentally.[27]

Forming granulation tissue and callus and

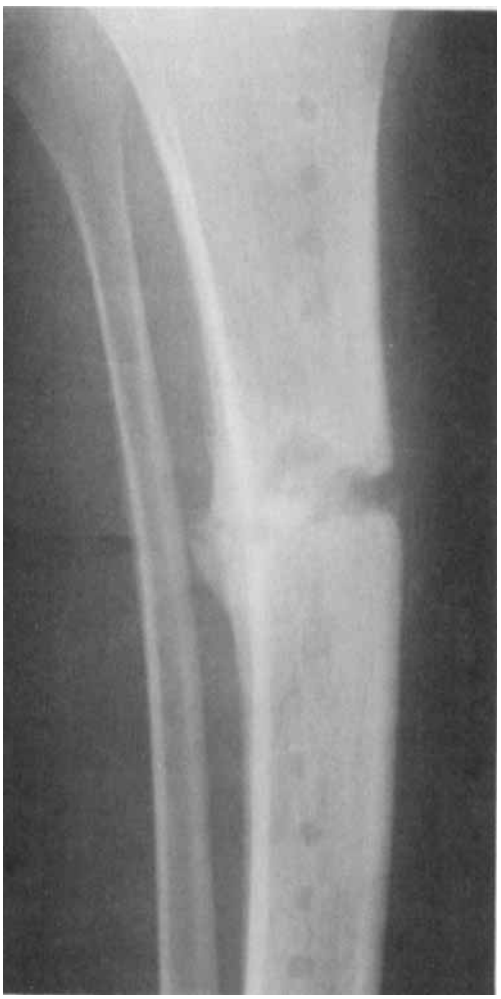


FIG. 3. RAP versus disuse osteoporosis. This transverse tibial fracture was immobilized in an external fixator for approximately three months, after which the fixator was removed and this roentgenogram taken in preparation for changing the treatment because of delayed union and loosening of the fixation pins. The pin holes are visible. Note the longitudinal tunneling of compacta in each major tibial fragment due to BMU-based osteonal bone remodeling that has increased well over five times above normal. This illustrates the effect of the RAP caused by both the original fracture plus drilling five pins into the proximal fragment and four into the distal one. Note also the lack of such tunneling in the fibula, which was not fractured but did experience the same degree of mechanical disuse during the previous three months. The differences in such tunneling between the fibula and tibia show that the disuse osteoporosis typically held as the sole cause of the tunneling and increased turnover of the tibia cannot be the sole cause. Because of the increased bone formation, which is a part of the increased turnover, a scintigram of this tibia would be warm or even hot but that of the fibula, cool. Note finally that there is a small amount of callus on the posterior cortices that lies in contact, but that none is present in the anterior gap. That is an effect of distraction, in turn due to incomplete reduction while in the fixator.

beginning the remodeling and modeling activities require activating previously dormant local precursor cells. Activation in the present sense is defined as sensitization and effective stimuli yielding the appropriate response. This activation makes the precursor cells begin to produce new cell populations. Some of those new cells differentiate and organize into vessels, supporting cells, fibroblasts, chondroblasts, chondroclasts, osteoclasts, and osteoblasts. The osteoblasts finally produce and initiate mineralization of the organic matrices of new bone and cartilage. The osteoclasts are essential to the replacement of callus by lamellar bone and to the modeling process. Motion at a healing fracture tends to accentuate cartilage formation, and absolute fixation tends to minimize it,[2,9,50,58,64,66,74] but, for clinical purposes, both healing modes function well in the overall healing process.

These facts convey the message that the activation–differentiation–organization processes control where bone healing occurs, in addition to if, when, how much, how fast, and how long. The differentiation–organization processes (the latter are usually ignored by experimentalists but are always in evidence) control what kind of structural matrix is formed. Illuminating discussions of these matters were published recently by Parfitt,[48] Sachs,[55] and Urist *et al.*,[73] and were also discussed at the 1987 University of Utah-sponsored Workshop on Bone Biology.

At the moment of a fracture, bone graft, osteotomy, or arthrodesis, the local tissues

contain very few osteoblasts and no chondroblasts. Published histomorphometric data show that, if only the preexisting osteoblasts had to heal a femoral shaft fracture, they would need between 200 and 1000 years to make enough bone to do it, if they lived that long. Since their functional lifetimes in humans are only two to three months,[24,33,34,43,51] successful and prompt bone healing mandates increasing their numbers by many thousands, and only the mediator mechanisms do that. The osteoblasts' short functional life spans also mean the mediator mechanisms must replace exhausted osteoblasts with new ones during the many months needed to heal a fracture, arthrodesis, osteotomy, or bone graft completely.

The successes reviewed by Goldberg and Stevenson[28] and Osterman and Bora[47] of vital bone grafts transferred from donor to recipient sites with circulation still intact may reflect the effects of the graft's still competent and viable mediator mechanisms rather than of any still-viable osteoblasts. All other kinds of bone grafts are in effect infarcted dead bone as Burchardt[10] and Friedlaender[20] note, so their success should depend mostly on the competence of the mediator mechanisms in the recipient site.

Many priming, mitogenic, differentiating, and organizing agents participate in enabling and controlling each healing stage, and inhibitor agents probably also participate. Table 2 lists a few such substances currently under study[54] that participate in the local autocrine and paracrine communication defined below. One should add to them the local bioelectric effects studied by many investigators and perhaps other yet unsuspected physical and membrane-permeability effects. The details of what controls the whole healing process are much more complex than was suspected ten or more years ago.

It has become increasingly clear that most bone healing failures not due to improper treatment stem from abnormalities in the activation–differentiation–organization processes rather than from faults in existing osteoblasts. Since osteoblasts (like osteoclasts) do not produce or replicate themselves or determine where, when, and how many of them will be produced, it falls to the mediator mechanisms to provide these essential functions and also any failures or other aberrations of these functions. Today, few experienced bone pathologists or cell biologists would contest these observations.[3–6,8,29,31–35,41,43,66,78] In different words, a fracture that heals with four times more callus than another similar one usually produces four times more capillaries, osteoblasts, and supporting cells, rather than similar numbers of osteoblasts that worked four times faster or more in the final event.

TABLE 2. Some Currently Studied Labile Growth Factors, Mitogens, and Differentiating Agents

| | |
|---|---|
| Prostaglandin $PGE_1$ | Fibronectin |
| Prostaglandin $PGE_2$ | $Interleukin_1$ |
| Somatomedins | $Interleukin_2$ |
| Bone morphogenetic protein | Platelet growth factor |
| Epidermal growth factor | Tumor necrosis factor |
| Varied angiogenic growth factors | Osteoclast-activating factor |
| | Bradykinins |
| | Undiscovered processes |

Part II of this work will suggest how this property relates to the strategy of research on healing problems, including those of soft tissues.[27] This property also suggests caution by clinicians urged by a pharmaceutical house to try a new drug on human bone healing problems because in tissue culture it stimulates osteoblasts in fetal rat calvaria or femurs. Those *in vitro* systems do not contain the intact mediator mechanisms, so they do not show how the living person will react to an agent.[24] A recent paper adds authoritative multinational weight to that observation,[18] and Part II will address this issue in more detail.[27]

Beginning with the fracture itself, com-

pleting each healing stage seems somehow to activate its successor, which implies local communication between the various components of the local tissues.[24,73] When a cell generates its own messenger to control its own activity, the process is called an autocrine effect. When a cell communicates with neighboring cells, the process is called a paracrine effect. Autocrine–paracrine effects probably exert more control over bone healing sequences than systemic agents such as hormones, vitamins, and mineral ions in the blood.

General pathologic experience shows that, in some situations, each bone healing stage can arise alone without being caused by a fracture.[5,8,31,49] As examples, in myositis ossificans, myelofibrosis, Paget's disease, and under normal growth plates, woven bone formation occurs without a fracture, and in the latter three cases without mechanical injury. In some osteomas of the calvarium, lamellar bone modeling formation drifts occur without previous mechanical injury and in the absence of large mechanical bone loads, strains, and stresses. Cartilage can form *de novo* in soft tissues such as ecchondromas and in the bundle of His in the heart. BMU-based remodeling normally replaces the mineralized cartilage of growth plates with woven bone in the absence of local trauma, and likewise for the normal replacement of primary spongiosa by secondary spongiosa. In many cases of algodystrophy (migratory osteoporosis), a RAP occurs without an inciting fracture or other injury. Bone resorption modeling drifts can completely remove cortical bone in "disappearing bone disease" without being caused by any known local injury or mechanical bone-loading abnormality. Finally, granulation tissue routinely arises in other conditions such as incisions, chronic skin ulcers, or during healing of infections that do not involve bone without leading to subsequent bony callus formation. To reiterate, in conditions other than bone healing, each of the normal bone healing stages can occur alone without following its usual predecessor and without preceding its usual successor in normal bone healing.

Such facts suggest that different agents can activate and control each bone healing stage. One clinical meaning of this is that many different drugs may affect bone healing by acting in different ways on one or another healing stage.

Furthermore, any stage in bone healing can malfunction separately from the others. This also suggests that, whatever the controls have in common, each can respond to some things that have little or no effect on the others. Part II of this work will provide examples of such malfunctions.

During bone healing, the callus and any recently healed fracture remain mechanically flexible, so processes influenced by local mechanical bone loads receive larger such messages during mechanical usage of the limb than they do years after the fracture has healed when the bone has regained normal stiffness and normal function.[23,24] This early flexibility stems partly from the months that new bone needs to mineralize fully after its histologic formation finishes. The flexibility increases the rapidity of the modeling phase and helps the modeling activity fit the architecture of the finally healed fracture to its typical mechanical demands or usage (see papers referred to in Cowin *et al.*[14] and by Frost[25,26]).

For several reasons, histologic sections can show different healing stages in progress in different places in a given fracture. That is, one microscopic field could show chondrogenesis, another *de novo* woven bone formation, yet another replacement of earlier formed woven bone by lamellar bone, and another some still-organizing hematoma. Still, in any single domain a few tens of microns across, the sequences described above usually occur. This overlap means that, at some moment during the healing process, a drug could affect several of its separate stages at the same time, so several different kinds of drug effects could combine to cause the ultimate clinically observed result.

The above background suggests a rationale for classifying, treating, and studying bone healing problems. Part II of this work discusses and illustrates them.[27]

## REFERENCES

1. Aegerter, E. E., and Kirkpatrick, J. A.: Orthopaedic Diseases, ed. 4. Philadelphia, W. B. Saunders, 1975.
2. Albright, J. A., and Brand, R. A. (eds.): The Scientific Basis of Orthopaedics, ed. 2. Norwalk, Connecticut, Appleton and Lange, 1987.
3. Anderson, C.: Personal communications, 1984–1987.
4. Anderson, M. A.: Personal communication, 1987.
5. Anderson, W. A. D., and Kissane, J. M.: Pathology, ed. 7. St. Louis, C. V. Mosby, 1977.
6. Arnold, J. S.: Personal communications, 1969–1987.
7. Auxhasen, G.: Histologische Untersuchunger uber knochen Transplantation am Menschen. Dtsch. Z. Chir. 91:388, 1907.
8. Bogomull, G. P., and Schwamm, H. A.: Orthopaedic Pathology. Philadelphia, W. B. Saunders, 1984.
9. Brand, R. A., and Rubin, C. T.: Fracture healing. *In* Albright, J. A., and Brand, R. A. (eds.): The Scientific Basis of Orthopaedics, ed. 2. Norwalk, Connecticut, Appleton and Lange, 1987, pp. 325–345.
10. Burchardt, H.: The biology of bone graft repair. Clin. Orthop. 174:28, 1983.
11. Burr, D. B., Martin, R. B., Schaffler, M. B., and Radin, E. L.: Bone remodeling in response to *in vivo* fatigue microdamage. J. Biomech. 18:189, 1985.
12. Casagrande, P., and Frost, H. M.: Fundamentals of Clinical Orthopaedics. New York, Grune and Stratton, 1953.
13. Courpron, P.: Bone tissue mechanisms underlying osteoporoses. Orthop. Clin. North Am. 12:513, 1981.
14. Cowin, S. C., Lanyon, L. E., and Rodan, G.: The Kroc Foundation Conference on Functional Adaptation in Bone Tissue. Calcif. Tissue Int. 36[Suppl.]:1, 1984.
15. Daum, W. J., Simmons, D. J., Fenster, R., and Shively, R. A.: Radiostrontium clearance and bone formation in response to simulated internal screw fixation. Clin. Orthop. 219:283, 1987.
16. Davis, R. F., Jones, L. C., and Hungerford, D. S.: The effect of sympathectomy on blood flow in bone. J. Bone Joint Surg. 69A:1384, 1987.
17. Duncan, C. P., and Shim, S.: The autonomic nerve supply of bone. J. Bone Joint Surg. 59B:323, 1979.
18. Evans, R., Czitober, H., Copp, H., Minczel, J., Fujita, T., and Bijvoet, O.: Is there a need for whole body physiology? Bone Miner. 2:243, 1987.
19. Frame, B., Parfitt, A. M., and Duncan, H. (eds.): Clinical Aspects of Metabolic Bone Disease. Amsterdam, Excerpta Medica, 1973.
20. Friedlaender, G. E.: Bone grafts: The basic science rationale of clinical applications. J. Bone Joint Surg. 69A:786, 1987.
21. Frost, H. M.: Mathematical Elements of Lamellar Bone Remodelling. Springfield, Illinois, Charles C Thomas, 1964.
22. Frost, H. M.: Orthopaedic Biomechanics. Springfield, Illinois, Charles C Thomas, 1973.
23. Frost, H. M.: The regional acceleratory phenomenon: A review. Henry Ford Hosp. Med. J. 31:3, 1983.
24. Frost, H. M.: Intermediary Organization of the Skeleton. Boca Raton, Florida, CRC Press, 1986.
25. Frost, H. M.: Structural adaptations to mechanical usage. A proposed "three-way rule" for BMU-based remodeling of lamellar bone. Part I. Veterinary and Comparative Orthopaedic Traumatology 1:9, 1988.
26. Frost, H. M.: Structural adaptations to mechanical usage (SATMU): (2). Redefining Wolff's law: The remodeling problem. Anat. Rec. (in press).
27. Frost, H. M.: The biology of fracture healing: An overview for clinicians. Part II. Clin. Orthop. 248:294, 1989.
28. Goldberg, V. M., and Stevenson, S.: Natural history of autografts and allografts. Clin. Orthop. 225:7, 1987.
29. High, W. B.: Personal communication, 1987.
30. Hori, M., Takahashi, H., Konno, T., and Haba, T.: A classification of *in vivo* bone labels after double labelling in canine bone. Bone 6:147, 1985.
31. Jaffe, H.: Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints. Philadelphia, Lea & Febiger, 1972.
32. Jaworski, Z. F. G.: Lamellar bone turnover system and its effector organ. Calcif. Tissue Int. 36[Suppl.]:46, 1984.
33. Jaworski, Z. F. G.: Does the mechanical usage inhibit bone "remodeling?" Calcif. Tissue Int. 41:239, 1987.
34. Jee, W. S. S.: The skeletal tissues. *In* Weiss, L. (ed.): Cell and Tissue Biology. A Textbook of Histology. 6th ed. Baltimore, Urban and Schwarzenberg, 1988, pp. 211–254.
35. Johnson, L. C.: The kinetics of skeletal remodeling. *In* Milch, R. A., and Robinson, R. A. (eds.): Structural Organization of the Skeleton. New York, National Foundation March of Dimes, 1964, pp. 66–142.
36. Kolář, J., Babicky, A., and Vrabec, R.: The Physical Agents and Bone. Prague, Czechoslovakia, Czechoslovac Academy of Sciences, 1965.
37. Laumen, E. L., and Kelly, P. J.: Blood flow, oxygen consumption, carbon dioxide production and blood calcium and pH changes in tibial fractures of dogs. J. Bone Joint Surg. 51A:298, 1969.
38. Lavine, L. S., and Grodzinski, A. J.: Electrical stimulation of bone. J. Bone Joint Surg. 69A:626, 1987.
39. Luck, J. V.: Bone and Joint Diseases. Springfield, Illinois, Charles C Thomas, 1950.
40. MacAllister, J.: Personal communication, 1987.
41. Martin, R. B.: Osteonal remodeling in response to screw implantation in canine femora. J. Orthop. Res. 5:445, 1987.
42. McLean, F. C., and Urist, M. R.: Bone: An Introduction to the Physiology of Skeletal Tissue, ed. 2. Chicago, University of Chicago Press, 1961.
43. Melsen, F., and Mosekilde, L.: The role of bone

biopsy in the diagnosis of metabolic bone disease. Orthop. Clin. North Am. 12:571, 1981.
44. Miller, M. R., and Kasahara, M.: Observations on the innervation of human long bones. Anat. Rec. 145:13, 1963.
45. Nilsson, O. S., Urist, M. R., Dawson, E. G., Schmalzried, T. P., and Finerman, G. A. M.: Bone repair induced by bone morphogenetic protein in ulnar defects in dogs. J. Bone Joint Surg. 68B:635, 1986.
46. Norrdin, R. W.: Personal communication, 1988.
47. Osterman, A. L., and Bora, F. W.: Free vascularized bone grafting for large-gap nonunions of long bones. Orthop. Clin. North Am. 15:131, 1984.
48. Parfitt, A. M.: The cellular basis of bone remodeling: The quantum concept reexamined in light of recent advances in the cell biology of bone. Calcif. Tissue Int. 36[Suppl]:37, 1984.
49. Putschar, W. G. J.: General pathology of the musculoskeletal system. *In* Buchner, F., Letterer, E., and Roulet, F. (eds.): Handbuch der Algemeinen Pathologie. Berlin, Springer-Verlag, 1960, pp. 361–486.
50. Rahn, B.: Bone healing: Histologic and physiologic concepts. *In* Sumner-Smith, G. (ed.): Bone in Clinical Orthopaedics. Philadelphia, W. B. Saunders, 1982, pp. 335–385.
51. Recker, R. R. (ed.): Bone Histomorphometry. Techniques and Interpretation. Boca Raton, Florida, CRC Press, 1983.
52. Rhinelander, F. W.: Tibial blood supply in relation to fracture healing. Clin. Orthop. 105:34, 1974.
53. Rhinelander, F. W., and Wilson, J. W.: Blood supply to developing, mature and healing bone. *In* Sumner-Smith, G. (ed.): Bone in Clinical Orthopaedics. Philadelphia, W. B. Saunders, 1982, pp. 81–158.
54. Rosier, R. N.: Orthopedic basic science: Update. Orthopedics 10:1793, 1987.
55. Sachs, L.: The molecular control of blood cell development. Science 238:1374, 1987.
56. Schaffler, M. D.: Stiffness and fatigue of compact bone at physiological strains and strain rates. Thesis, University of West Virginia, Morgantown, West Virginia, 1985.
57. Schenk R. K.: Fracture repair overview. *In* Ninth European Symposium on Calcified Tissues. Vienna, Facta Publication, 1973.
58. Schenk, R. K.: Personal communication, 1984.
59. Schenk, R. K., and Perren, S. M.: Biologie und Biomechanik der Frakturheilung am Rohrenknochen als Grundlage der Osteosynthese. Hefte Unfallheilk. 129:29, 1977.
60. Schenk, R. K., and Willenberger, H.: Zur Histologic der Primaren Knochenheilung Modifikationen und Grenzen der Spaltheilung in Abhangigkeir von der Defektgrosse. Hefte Unfallheilk. 80:155, 1977.
61. Schenk, R. K., and Willenegger, H.: Sum histologischen Bild der sogenannten Primarheilung der Knochen kompakta hach experimentellen Osteotomies am Hund. Experientia 20:593, 1963.
62. Schnitzler, C. M., and Solomon, L.: Histomorphometric analysis of a calcaneal stress fracture: A possible complication of fluoride therapy for osteoporosis. Bone 7:193, 1986.
63. Shih, A. S., and Norrdin, R. W.: Regional acceleration of remodeling during healing of bone defects in beagles of various ages. Bone 6:377, 1985.
64. Simmons, D. J.: Fracture healing. *In* Urist, M. R. (ed.): Fundamental and Clinical Bone Physiology. Philadelphia, J. B. Lippincott, 1980, pp. 283–330.
65. Sumner-Smith, G. (ed.): Bone in Clinical Orthopaedics. Philadelphia, W. B. Saunders, 1982.
66. Sumner-Smith, G., and Bishop, H. M.: Nonunion of fractures. *In* Sumner-Smith, G. (ed.): Bone in Clinical Orthopaedics. Philadelphia, W. B. Saunders, 1982, pp. 399–427.
67. Takahashi, H. (ed.): Handbook of Bone Morphometry. Niigata, Japan, Nishimura, 1985.
68. Takahashi, H., Togawa, Y., Hanaka, T., Watanabe, G., Saitoh, Y., and Suzuki, H.: The effects of various types of microelectrical current wave form on bone formation in internal remodeling in dogs. *In* Fukada, E., Inoue, S., Sakou, T., Takahashi, H., and Tsuyama, N. (eds.): Bioelectrical Repair and Growth. Niigata, Japan, Nishimura, pp. 184–191, 1985.
69. Takahashi, H., Watanabe, G., Togawa, Y., Hanzoka, T., Kono, T., Sarto, Y., and Suzuki, H.: The effects of various types of electrical current on internal remodeling of bone in dogs. Orthop. Trans. 2:369, 1982.
70. Uhthoff, H. (ed.): Current Concepts of Bone Fragility. Berlin, Springer-Verlag, 1986.
71. Urist, M. R. (ed.): Fundamental and Clinical Bone Physiology. Philadelphia, J. B. Lippincott, 1980.
72. Urist, M. R.: Personal communication, 1985.
73. Urist, M. R., DeLange, R. J., and Finerman, G. A. M.: Bone cell differentiation and growth factors. Science 220:680, 1983.
74. Urist, M. R., and McLean, F. C. C.: Bone repair in rats with multiple fractures. Am. J. Surg. 80:685, 1950.
75. Weinmann, J. P., and Sicher, H.: Bone and Bones, ed. 2. St. Louis, C. V. Mosby, 1955.
76. Weiss, L. (ed.): Histology, ed. 5. New York, Elsevier-North Holland, 1983.
77. Wolff, J.: Das Gesetz der Transformation der knochen. Berlin, A. Hirschwald, 1892.
78. Woodard, C.: Personal communication, 1987.