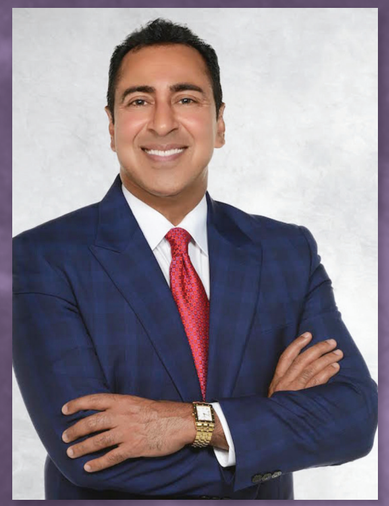

In the second edition of this best-selling book, Dr Garg rejects the salesmanship that often swirls around PRP/PRF and instead focuses on the science, biology, and clinical applications of this natural biomaterial. Credited as a co-discoverer of PRP, he knows how to break down the science and explain how autologous blood concentrates work to speed healing and promote tissue regeneration. This natural, inexpensive, and safe material has enormous potential in a dental clinic, and Dr Garg wants to make sure every clinician has access to information that is easy to digest and easy to apply. This book is thereby a roadmap to incorporating autologous blood concentrates into clinical practice. The early chapters focus on the biology of what goes on when blood is collected and centrifuged and reintroduced into wound sites as well as how to prepare the different formulations of autologous blood concentrates. The later chapters demonstrate how to use this material in implant surgery, soft and hard tissue healing, facial cosmetics, and other clinical applications to achieve superb outcomes. With a bonus chapter on phlebotomy, this book is the practical manual novices need and experienced clinicians value.

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Autologous Blood Concentrates

Second Edition

Arun K. Garg, DMD

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Autologous Blood Concentrates

Second Edition

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Preface

In the nearly 25 years since Bob Marx and I developed the original formula for PRP, I have followed its gradual evolution from controversial idea to vital wound healing agent with keen interest—not unlike an anxious parent. In 2005, our co-authored book—*Dental and Craniofacial Applications of PRP* (Quintessence)—introduced the concept of platelet-rich plasma (PRP) to the world and provided scientific and clinical proof of its efficacy. Together, we spent the next decade training other clinicians on the proper use of PRP.

Everything changed in 2010, when it became public knowledge that PRP was the secret to Tiger Woods's speedy recovery from a torn ACL. Commercial interests quickly co-opted the conversation, drowning out the voices of those who, like Marx and me, did not want to see this low-cost biotechnology exploited by profit-hungry manufacturers of centrifuge devices. There was also an enormous amount of misinformation being promulgated by certain medical/dental experts who recognized the enormous therapeutic potential of autologous growth factors and seized the opportunity to establish a name for themselves in the scientific community. The medical literature became saturated with articles introducing new terminology to describe slightly modified growth factor compositions, often without much (if any) additional clinical benefit. The result was an alarming lack of standardization in protocols, a nomenclature best described as an alphabet soup of acronyms, and an overwhelming sense of confusion among clinicians. In 2015, when I published the first edition of this book, my primary motivation was to "set the record straight."

So the first edition of this book was my effort to refocus the conversation about platelet-derived therapies in order to make PRP accessible again to the practicing clinician. In titling the book, I made the major concession of using a generic term—autologous blood concentrates—as a way to signal my desire to focus on the science and not the politics. I wanted the book to reach clinicians regardless of which machine or nomenclature they were most familiar with.

In the world of regenerative biotechnology, 6 years is a very long time, and much has happened since the first edition of this book was published. This new second edition has been thoroughly revised, updated, and expanded to reflect current understanding, applications, and protocols of PRP for clinicians who have been using or wish to start using PRP in their practice. The centerpiece of this edition is a completely new chapter that details the step-by-step formulas and processes for preparing eight configurations of PRP and the specific indications for using each one. How and when to apply the various configurations in clinical dentistry—for soft tissue preservation, hard tissue preservation and regeneration, and facial rejuvenation procedures—is the subject of subsequent chapters. Because the use of PRP requires the clinician or an assistant to perform a venipuncture, the final chapter is a comprehensive guide to the principles and practice of phlebotomy.

I continue to engage in clinical PRP research, both in my private practices and through my charitable foundation, and will remain a passionate advocate for its use for the benefit of patients everywhere.

1

Autologous Blood Concentrates: The Science of Natural Wound Healing

In many ways, traditional surgery and the medical arts have always tried to remove barriers to natural wound healing. Removal of these barriers proved that through replicable conditions and cases, standardized protocols could be created and followed to enhance wound healing. Over time, replication of results led to even more standardized techniques and procedures. For example, wound debridement and administering antibiotics demonstrably helped prevent infection, and stabilizing wounds and placing tissues in closer physical proximity promoted healing. These particular kinds of standardized, replicable surgical techniques can be labeled assistive or nonobstructive.[1] However, beginning in the last quarter of the 20th century, a truly "proactive" phase in surgical medicine began with the discovery that macrophages, reacting with oxygen, release growth factors that promote wound healing.[2–6] An assortment of cellular/tissue and oxygen-related therapies followed,[7–16] culminating only about two decades ago in the use of growth factors produced from concentrated autologous blood platelets to promote wound healing.[17–22] The result is medical science's present focus on platelet and other biologic/regenerative therapies as critical means for promoting, initiating, and sustaining wound healing.[23]

In the mid-1980s, platelets were understood essentially as cells that helped to stop bleeding. Over the next 20 years, the discovery of the various growth factors released by platelets gave birth to regenerative medical therapies, most of which are still in their infancy.[24–35] How the growth factors and functional matrix delivered by autologous blood concentrates induce wound healing is widely understood. The focus of current research is replicating and standardizing the preparation and administration of the autologous-derived product to best suit the donor-patient. Though a variety of preparation techniques, products, and nomenclatures have been tried, the good news is that no significant difference in the osteogenesis of growth factors has been evidenced.[36–40]

Nevertheless, firmly establishing the science of platelet-rich plasma and other platelet-derived products requires an investigation of platelet biology, the release of growth factors, and the practical application for soft tissue healing and bone tissue regeneration. So far, the scientific journey of autologous blood concentrates has been remarkably expansive. The future of this journey promises to be more focused, even single-minded, toward its scientific destination—even more standardized products and procedures based on replicable results.

Platelet Biology

The first autologous blood concentrate was introduced in the literature as *autologous fibrin adhesive* and later changed to *platelet-rich plasma* (PRP). That term became standard, first in the oral surgery literature and then in all medical and dental surgical specialties. While many other terms have been used to describe autologous blood concentrates—particularly in niche markets as a way to sell specific centrifuges and/or test tubes—PRP will be used throughout this book.

As an actor in the performance of regenerative medicine,[41–47] PRP provides two of the three essential components for allowing a wound to heal in place: growth factors and a scaffolding stage (Fig 1-1). The third ingredient for

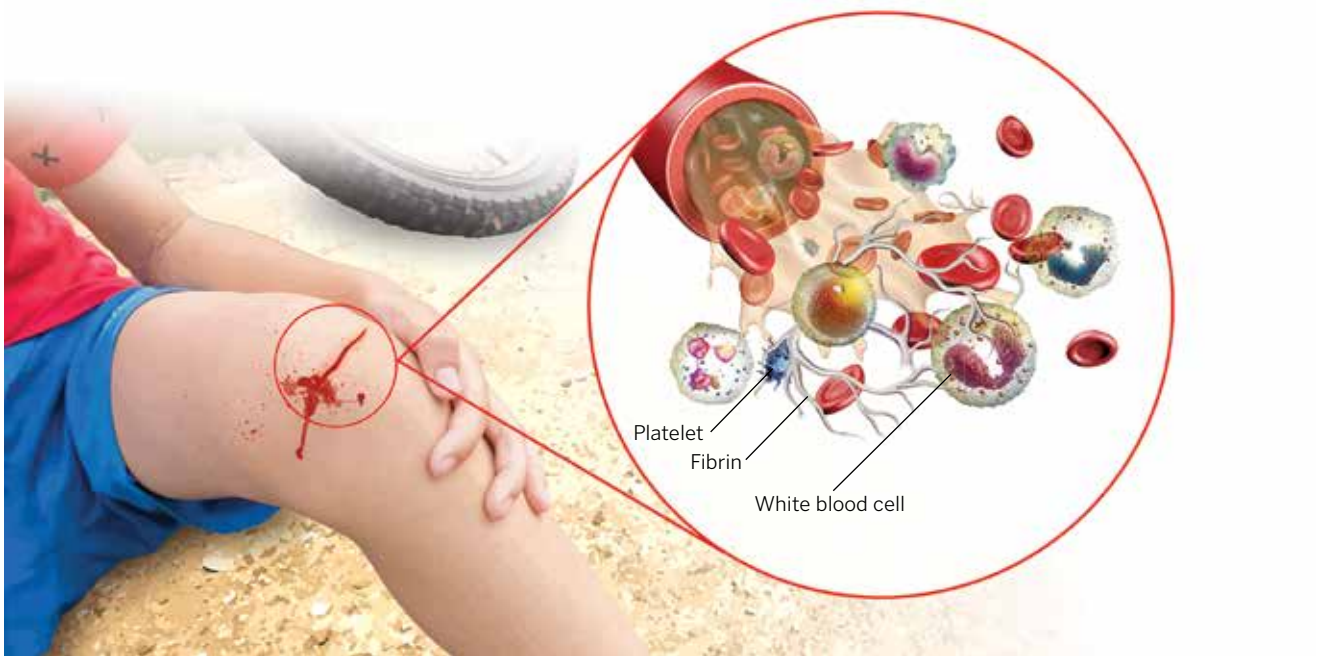

FIG 1-1 Components of blood that are concentrated in PRP.

in situ tissue regeneration is the cells. PRP is a patient's own blood concentrate, modified in a relatively quick, efficient, safe, and simple procedure, to obtain a dense concentration of platelets. The autologous nature of PRP precludes disease transmission to the patient or other adverse reactions. To provide wound healing benefit to the patient, PRP generally must have at least four to seven times the normal concentration of platelets, or roughly 1 million platelets per microliter.[48] A blood clot in a wound consists mostly of red blood cells and much smaller percentages of platelets and white blood cells (Fig 1-2). Applying PRP to such a wound essentially replaces red blood cells with growth factor–producing platelets and a fibrin network, thus (at least in theory) greatly enhancing the healing of wounds and migration of cells, as well as the regeneration of bone and soft tissue.

When bone marrow megakaryocytes undergo cytoplasmic fragmentation, the anuclear platelet cells enter the circulatory system. The relatively tiny platelet is about one-fourth the size of a red blood cell (approximately 8 μm in diameter) and six to seven times smaller than a lymphocyte; however, the platelet's membrane extends pseudopodially via invaginations, which provide an expansive, dynamic, and vigorous surface area for the cell membrane during activation.[1,49] The plasticity and resilience of the platelet's pseudopodic membrane enable its vascular-sealing qualities, along with its ability to form a thrombus and fibrin clot, as well as clot retraction when its hemostatic labors are complete[50] (Fig 1-3). Generally, the larger and younger the platelet, the greater its hemostatic qualities and the greater the quantities of growth factors contained within it.[23,51,52]

The short lives of platelets (240 hours or less) are very actively spent synthesizing and secreting growth factors as part of the blood-clotting process. The platelet contains lysosomes, ribosomes, mitochondria, and an assortment of intercellular proteins that help form its shape as well as its mobility. The platelet cell also contains storage organelles that consist of lysosomal granules (for storing enzymes for digestion), dense granules (for storing and secreting adenosine diphosphate [ADP]), and alpha granules (for summoning and activating other platelets via nascent growth factors) (Fig 1-4).[53–55]

The growth factors stored in the alpha granules include platelet-derived growth factor (PDGF) isomers labeled AA, BB, and AB (referred to as polypeptide "dimers" because

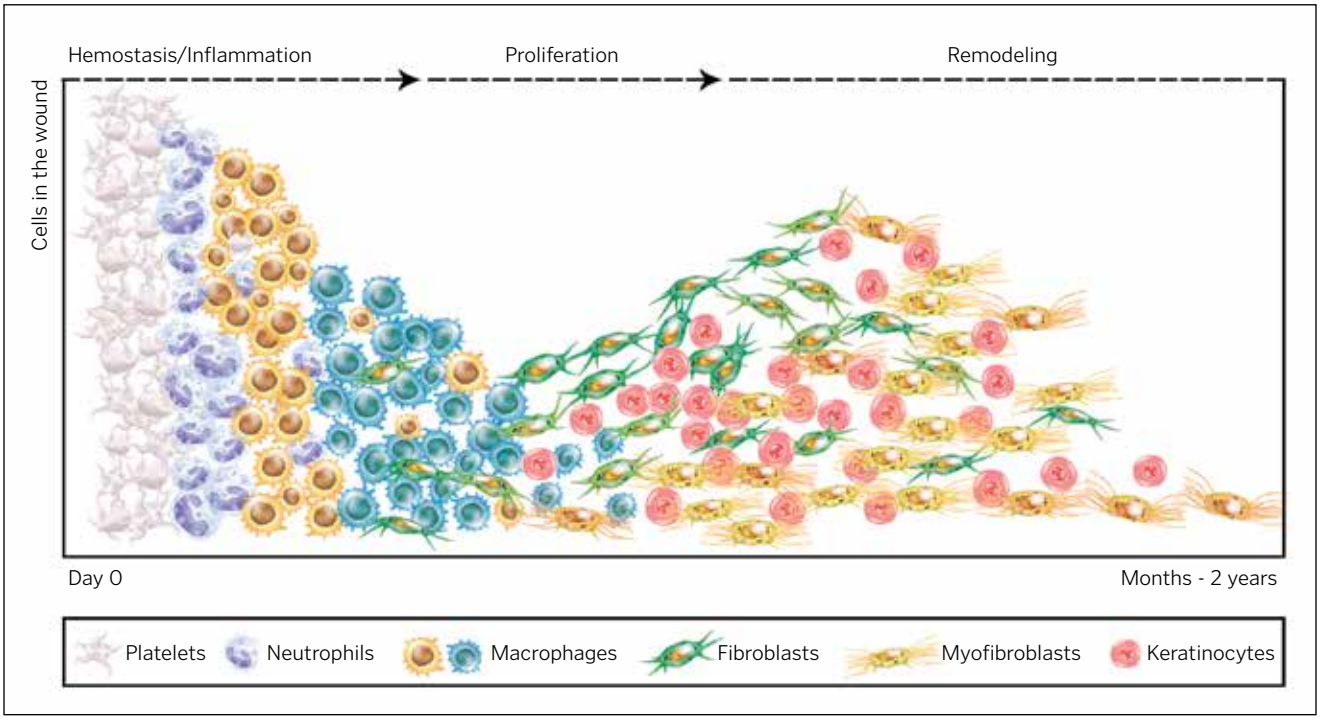

FIG 1-2 The classic wound healing cascade.

of their two active sites, which are actually antiparallel monomers); transforming growth factor (TGF) isomers beta 1 and 2; vascular endothelial growth factor (VEGF); and epithelial growth factor (EGF). Growth factors not contained in platelets include insulinlike growth factors (IGF) 1 and 2 and bone morphogenetic protein (BMP). The blood-clotting process activates the alpha granules in platelets to secrete growth factors, both when the platelets circulate normally in the blood and when the platelets are concentrated in PRP. Alpha granules move toward the membrane and bind themselves to its surface, causing histone and carbohydrate side chains to combine with, and to activate, growth factor proteins.[1]

In addition to their basic hemostatic roles, platelets have been found to play a number of nonhemostatic functions.[56,57] Tissue repair and inflammation are two of several functions that researchers are currently exploring.[58,59] The alpha granules in platelets are the producers/directors of the diverse roles medical science is learning platelets can play beyond the traditional role of hemostasis. Ironically, in fact, the granules contain substances that normally work in opposition to each other. The platelet's ability (when properly signaled) to release different substances specifically

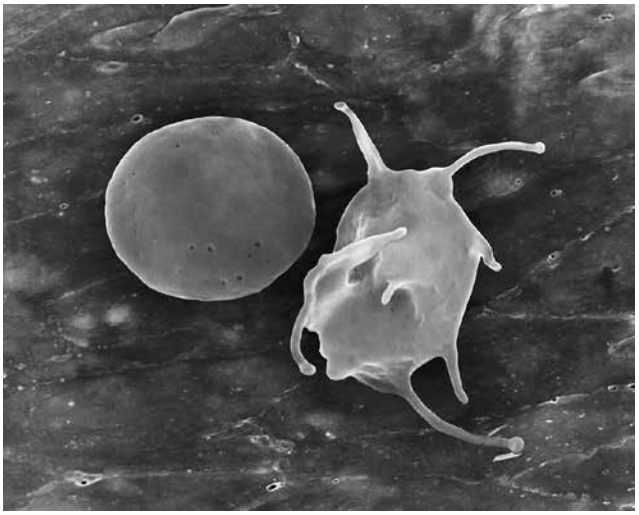

FIG 1-3 Scanning electron micrograph (SEM) appearance of a platelet before *(left)* and after *(right)* activation.

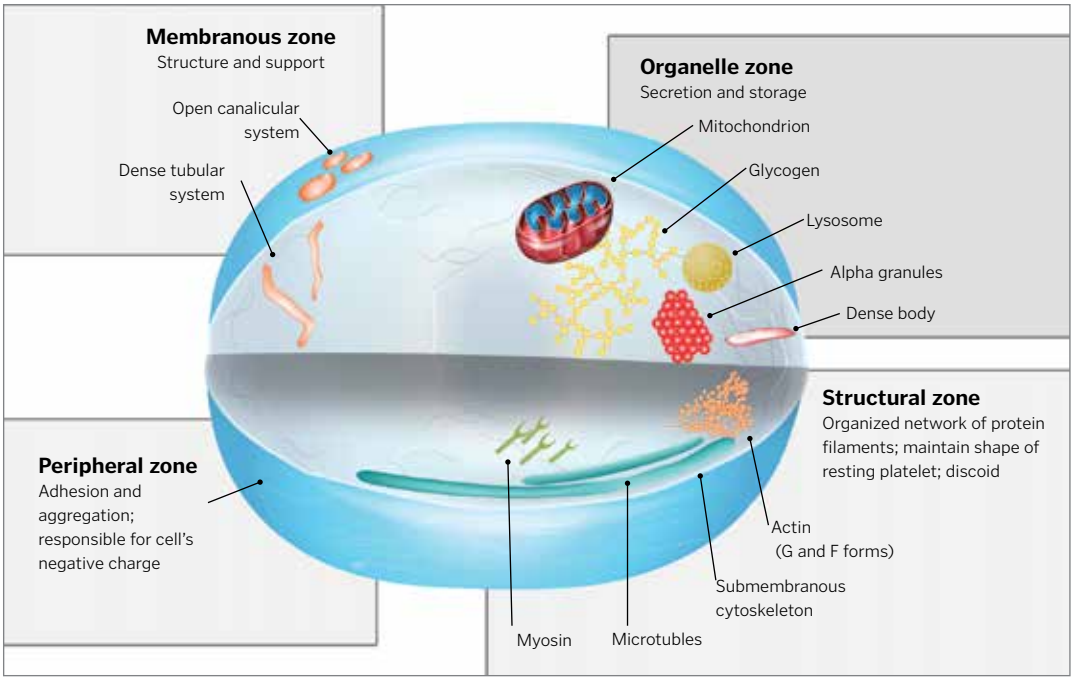

FIG 1-4 Shape and functions of platelet cells.

required by other cells, molecules, and tissues explains why it is the focus of so many different types of current medical research, including tissue inflammation and regeneration, neurology, autoimmunity, hemostasis, wound healing, atherosclerosis, and a diverse range of others.[60-66]

PRP Growth Factors

There are a number of different types of growth factors contained in platelets.[67-69] These growth factors are polypeptides, accounting not only for tissue and organ morphogenesis (from shortly after human conception to adulthood) but also for cell differentiation and proliferation. Their crucial activity in cell healing makes them especially important to current research in tissue engineering and regenerative medicine (Fig 1-5). The growth factors that have received the most attention from medical researchers and practitioners include PDGF-AA, PDGF-BB, and PDGF-AB; TGF-β1, TGF-β2, and TGF-β3; fibroblastic growth factor (FGF); IGF; EGF; and VEGF.

PDGF

PDGFs, found in several types of human cells but mostly in platelets, were the first type of growth factor discovered in alpha granules.[27] PDGF adheres only to target cells with receptive surface membranes. When a wound is treated with concentrated platelets, the release of PDGF triggers activity in fibroblasts, neutrophils, and macrophages, stimulating the latter to additionally release growth factors that help to heal injured tissues.[70-72] Specifically, the target cells' transmembrane receptors are activated by the platelet-released growth factors, and the receptors' intracytoplasmic qualities activate the signal transducer proteins, one of which migrates to the target cell's nucleus. There, the protein initiates a particular, regulated gene sequence—which may, for example, include the production of osteoid.

Alternatively, the sequence might lead to the synthesis of collagen. The regulated nature of the sequence precludes an "overdose" of concentrated growth factors. Growth factors' amutagenic qualities testify to their ability as natural proteins to initiate and participate in the regular genetic activities associated with the controlled mechanisms for wound healing.[1,73-76] As isomers of a single protein, and functioning as mitogens, PDGFs—the most common growth factors—perform different but often complementary tasks (Fig 1-6). This prompts certain cells to replicate, specifically mesenchymal stem cells, osteoblasts (producing osteoid), endothelial cells (secreting basal lamina), and fibroblasts (producing collagen).[77-83]

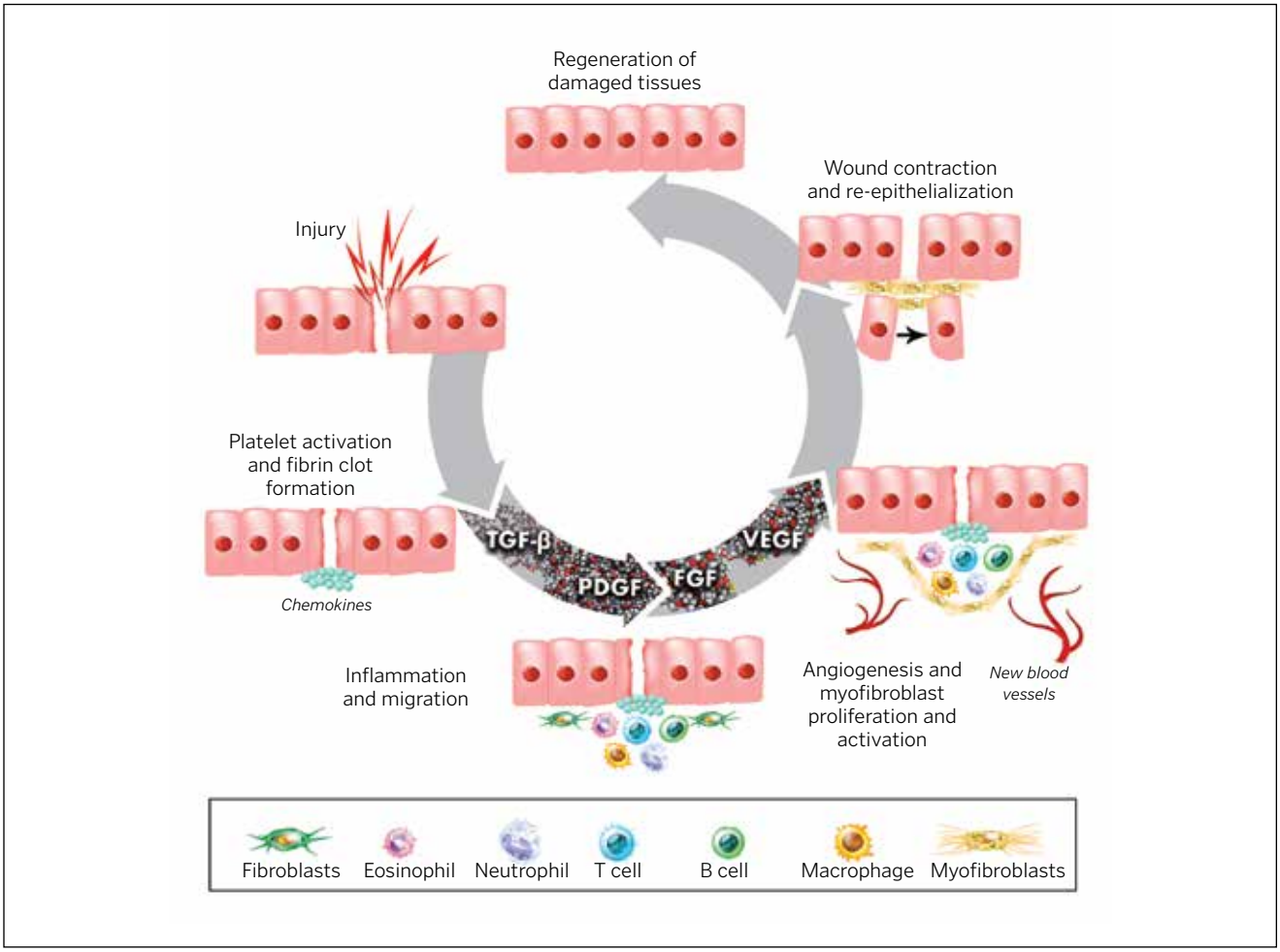

FIG 1-5 Wound healing and tissue regeneration cycle.

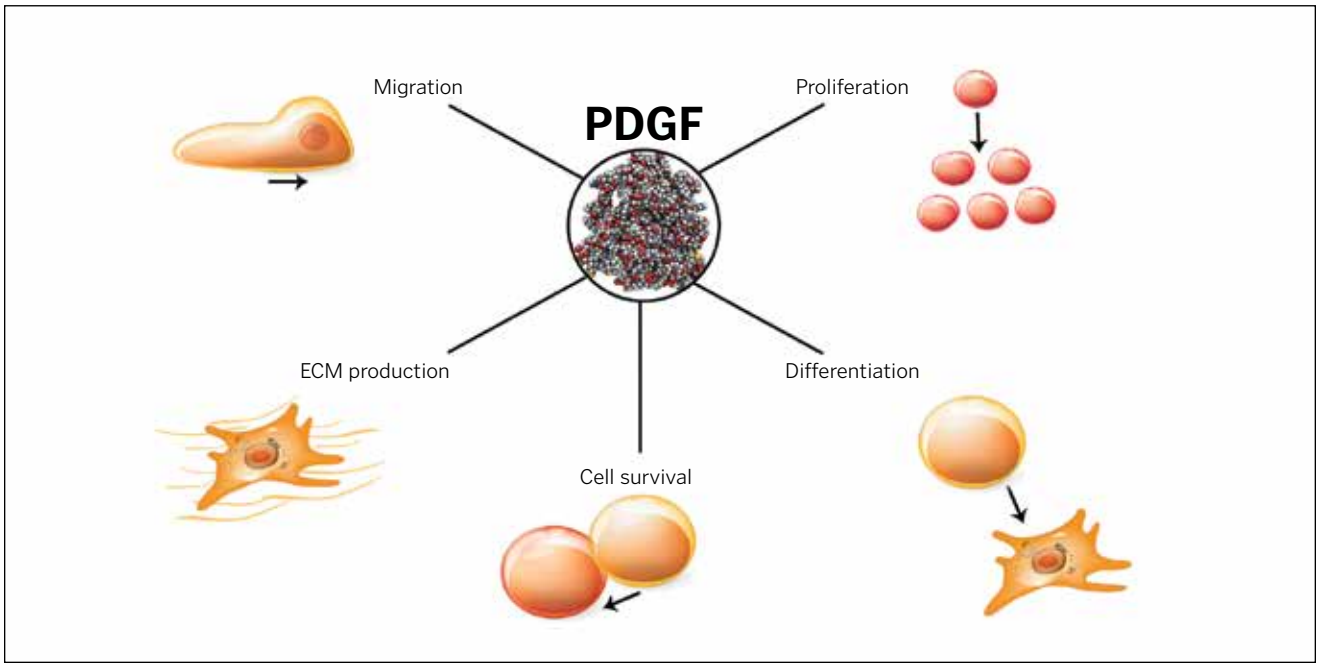

FIG 1-6 Roles of PDGF.

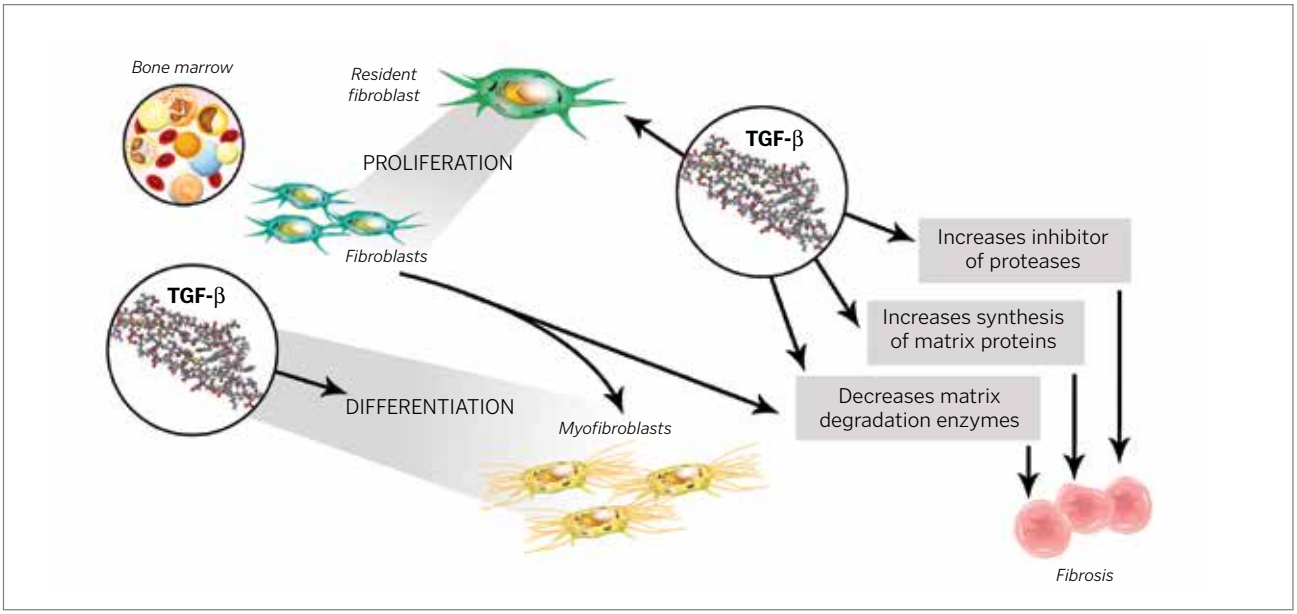

FIG 1-7 TGF-β stimulates the proliferation and migration of fibroblasts and the process of epithelial-mesenchymal transition, but it also stimulates fibrotic responses, which can lead to end-stage organ failure in the heart, kidney, etc.

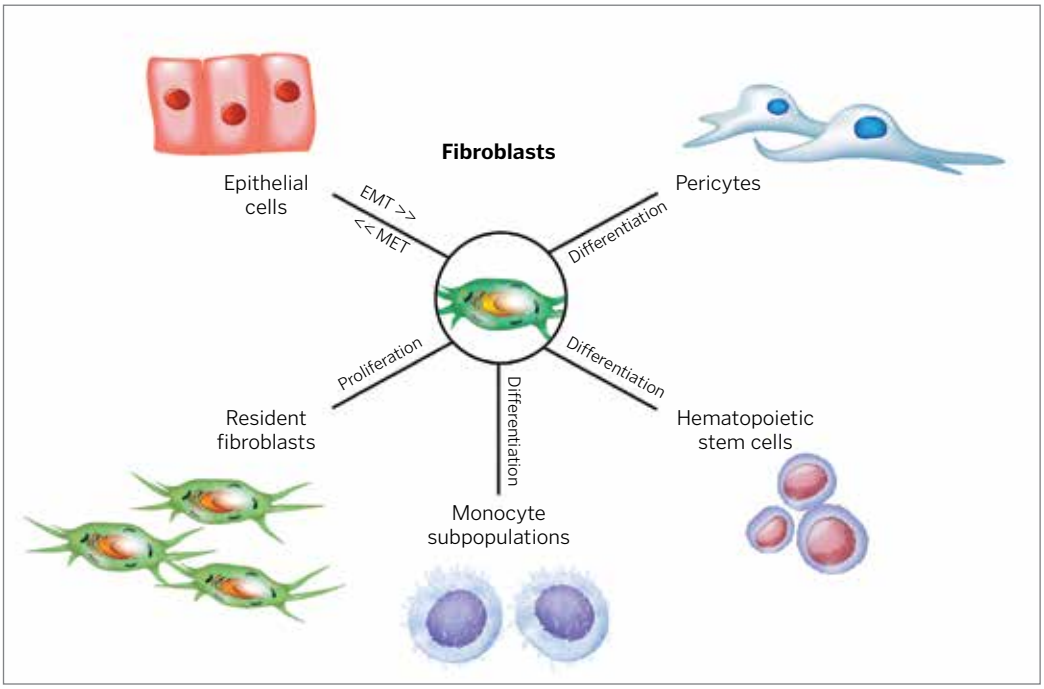

FIG 1-8 Fibroblasts have different origins at different developmental stages (EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition).

TGF-β1, TGF-β2, and TGF-β3

There are dozens of TGFs (including BMPs), and three of them (TGF-β1, TGF-β2, and TGF-β3) are protein growth factors that behave not only as mitogens (for cell replication) but also as morphogens (for cell differentiation).[84,85] As cell preservers, TGF-β factors serve essential functions in wound healing, from the fetus to the adult.[86–89] Like PDGFs, TGFs exert their influence in both healthy and pathologic cell activities, making their therapeutic use extremely problematic and challenging in that they often behave in opposite and even contradictory ways in both soft and hard tissues, including their roles in proliferation, migration, and differentiation[90–93] (Fig 1-7).

FGF

FGF is an important mitogen inducer of fibroblast and endothelial cell proliferation. It also stimulates angiogenesis and plays a vital role in the repair of skeletal muscles and tendons. New blood vessel formation is due in large part to the activities of FGF, and it stimulates the migration of the macrophage as well as epithelium for epidermis formation[40,94,95] (Fig 1-8).

IGF

IGFs are peptide hormones that have been found to promote cell growth in in vitro experiments. IGFs were also found to reduce levels of blood glucose in various tissues, hence their name. Their ability to stimulate glandular activities in humans differentiates them from other PRP growth factors. For example, IGF-1 mainly adheres to and stimulates receptors in cells of pituitary growth hormones. Most cells increase in size and number as a direct result of the synthesis and secretion of IGF-1 by tissues stimulated by growth hormones.

Growth factor production, along with growth hormone production and concentrations, wax and wane as part of the natural maturation process of humans before, during, and after pubescence, particularly for IGF-1. Liver production accounts for most IGF concentrations. IGFs have their most potent growth-stimulating effect on themselves and on nearby cells, and they (both IGF-1 and IGF-2) aid in bone cell mitosis. As an osteoblast secretion, IGF assists in osteogenesis and bone ossification via proliferation and differentiation of cells[96-98] (Fig 1-9).

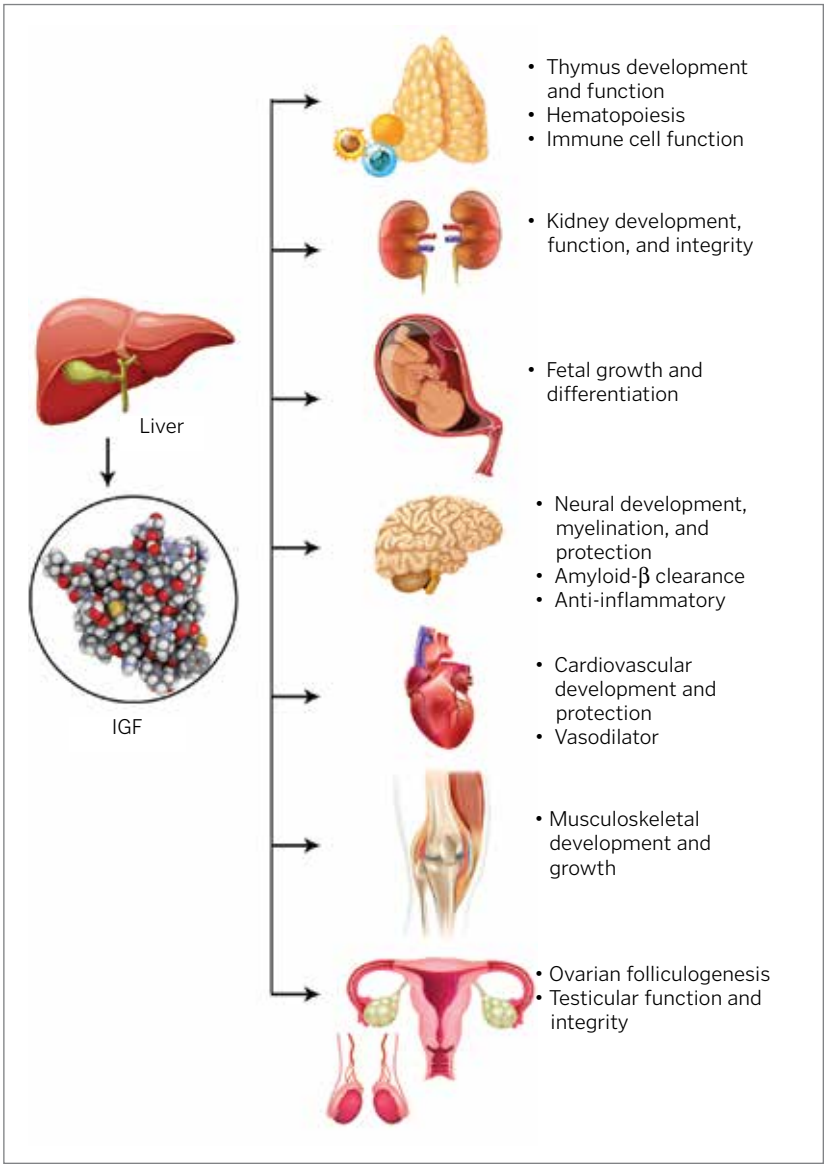

FIG 1-9 Some of the roles of IGFs.

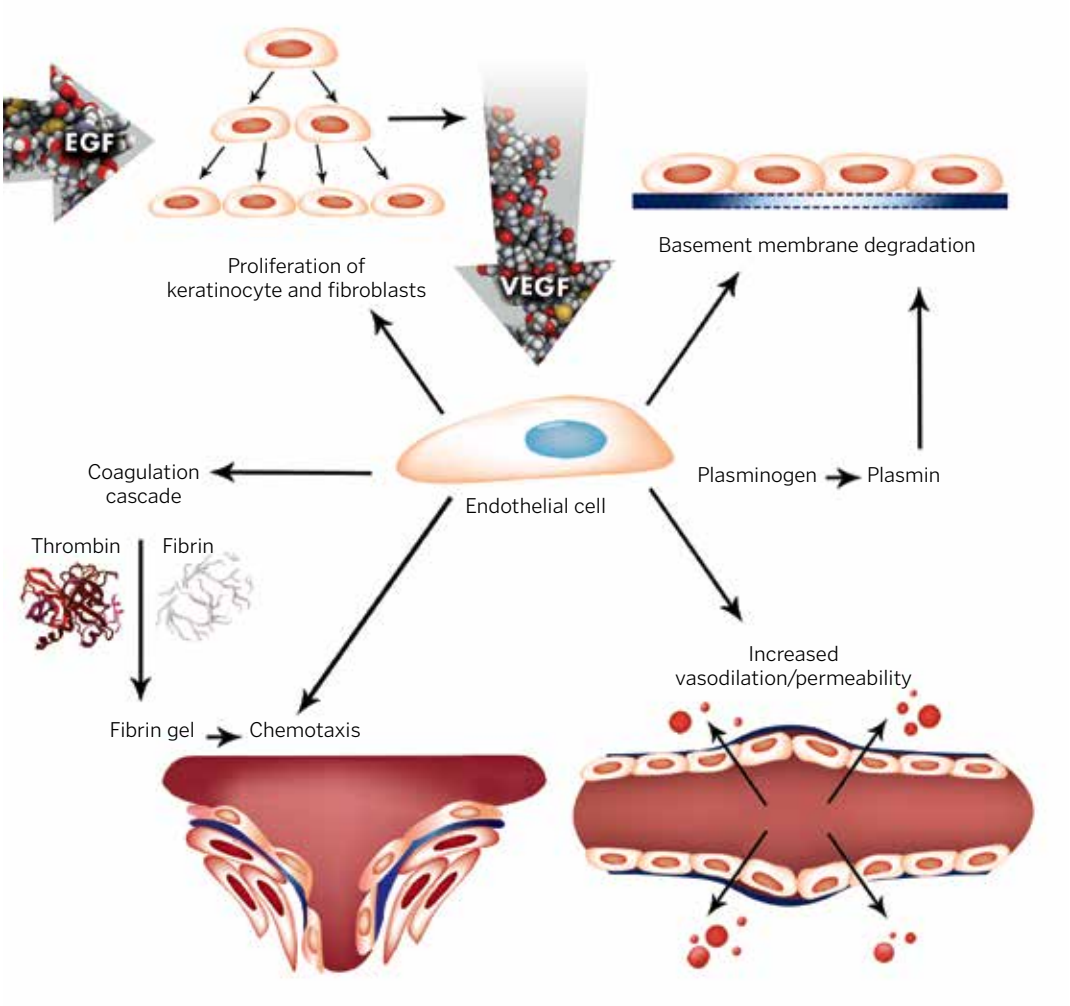

FIG 1-10 VEGF stimulates the endothelial cell, enhancing multiple phases of the angiogenic cascade.

EGF

The protein-based EGF causes the basal cells of the skin and mucous membranes to replicate, migrate, and form essential elements of these membranes.[99] EGF likely positively affects the generation of tissues as well as wound healing because of the way it controls the proliferation, growth, and migration of epithelial cells while strengthening the formation of new blood vessels. A therapeutic application of EGF has been used in preventing and treating dermatitis resulting from overexposure to x-rays or radium.

VEGF

As its name suggests, the protein-based VEGF helps to develop blood vessels by interacting with endothelial cells, stimulating the synthesis of basal lamina, and recruiting pericytes[69,100] (Fig 1-10). Like several other growth factors, VEGF is known for and studied scientifically mainly due to its activity in pathologic states rather than healthy ones. The role it plays in the formation of new blood vessels of cancerous tumors has provided much of what we know of its abilities to stimulate growth in other cells. Tumors, just like healthy cells, can synthesize growth factor proteins—including VEGF—that promote the formation of new blood vessels from existing ones (angiogenesis). Instead of angiogenesis taking place for normal body growth or tissue repair, in this pathologic process it enables the spread of cancerous cells. In this case, VEGF activity leads to the development of capillaries within the tumor because of its stimulation of endothelial cells, which are the raw materials needed for angiogenesis. Endothelial cell division leads to the growth and migration of the tumor cells, developing a cascade of shared growth factors between their cells. Possible cancer therapies, therefore, include ways to introduce proteins into the tumor that slow or stop angiogenesis.

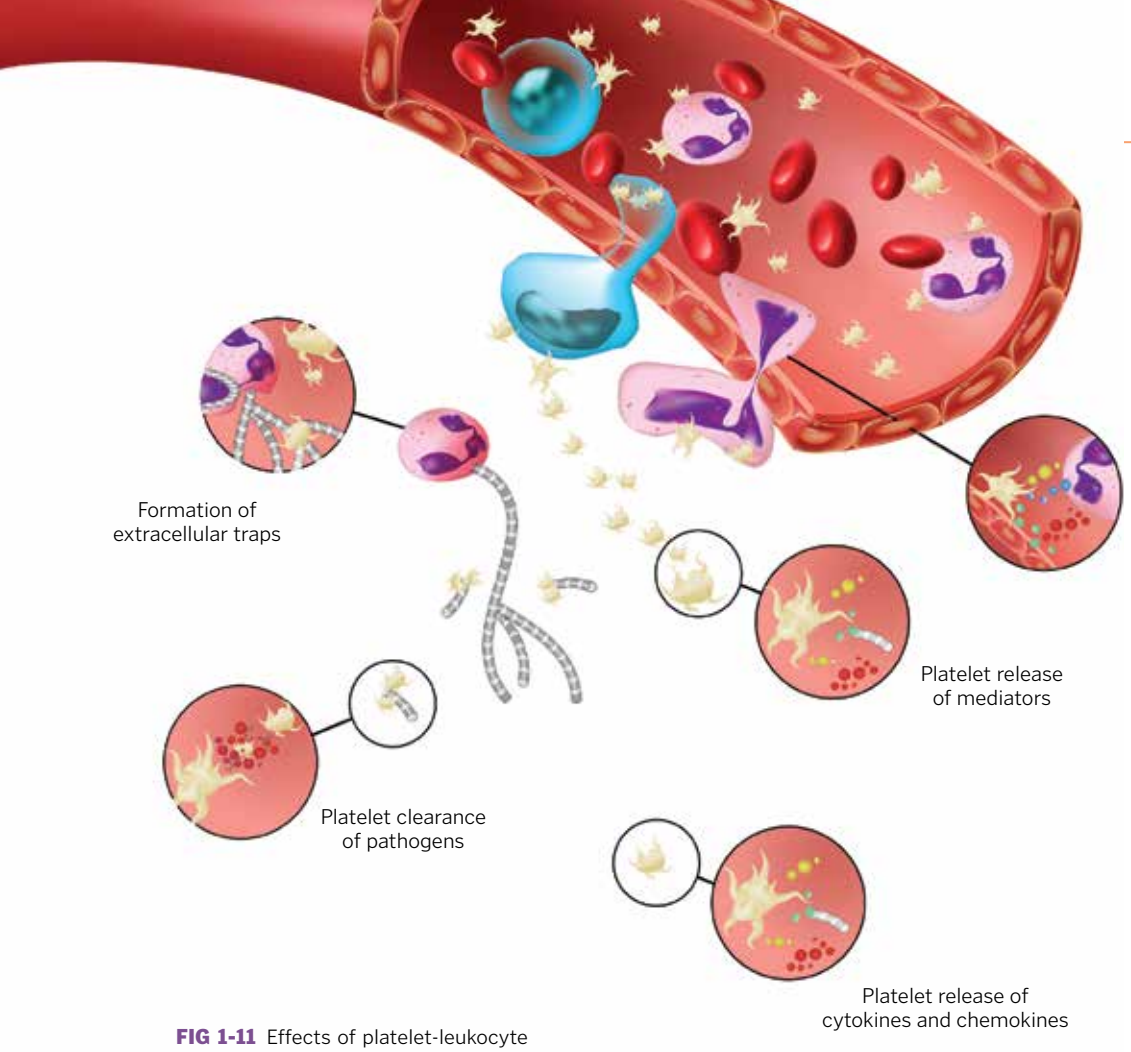

FIG 1-11 Effects of platelet-leukocyte aggregates on differentiation, activation, and cytokine release.

PRP and Soft Tissue Healing

PRP has shown great promise clinically and histologically, especially for healing soft tissue in a standard wound of a donor site for a split-thickness skin graft.[101,102] Additionally, healing therapies for burns may benefit significantly from PRP application. The platelets release growth factors and cell-signaling cytokines, such as interleukin and interferon, that act to regulate inflammation and infection in the immune system[103] (Fig 1-11).

When compared to non-PRP–assisted clotting, PRP-assisted clotting is remarkable for its rapidity of healing in the basal cells at the edge of the wound, where EGF induces epithelial proliferation; subsequent migration to the granulation tissue helps the clot's cell adhesion molecules. Unlike an unassisted clot, the PRP clot reveals the bundles of fibroblasts and collagen, evidence of an expanding epithelium, and more mature healing. This comparatively accelerated maturity is also evidenced by increasingly reduced vascularity and fibroblastic cellularity over time, as well as quicker fleshlike appearance in 2 to 6 months. Reduced pain in the first 7 days of the wound, and reduced scarring over time, are also notable differences effected by the PRP clot. These benefits are also demonstrated in healing of other soft tissue wounds, including mucosal flaps, dermal fat grafts, and similar wounds.[1]

Bone and soft tissue healing can be strengthened in a variety of surgical procedures when a concentrated mixture of autologous platelets is placed at the wound site. The relative ease of methods for obtaining PRP makes it an attractive regenerative adjunct therapy for many surgical treatments. Promoters of PRP tout its ability not only to help restore damaged bone and soft tissue but also to enhance wound healing, lower the patient's pain and discomfort after the surgical procedure, and reduce the rates of infection and loss of blood.[104–106] Much of the recent

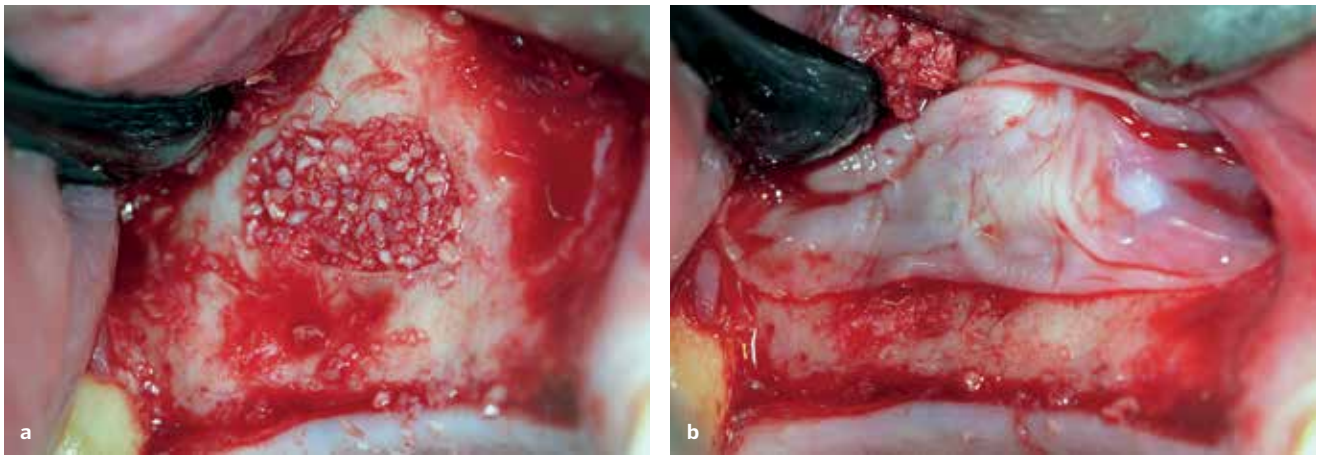

FIG 1-12 Application of PRP in a sinus elevation procedure. *(a)* Once an adequate volume of graft material hydrated with PRP liquid has been placed, the window is ready for a PRP membrane. *(b)* The PRP membrane is placed over the lateral window, and then the flap is sutured back in place.

literature on PRP has been devoted to its wide range of applications in tissue healing and repair, including maxillofacial, periodontal, oral (Fig 1-12), and plastic surgery; heart and spine surgery; and chronic ulcers of the skin and soft tissue.[107–110] Some studies have suggested that in addition to enhancing wound healing, PRP provides antimicrobial qualities to inhibit postoperative infections in oral surgery.[111] PRP has been used in such soft tissue therapies as ligament, muscle, and tendon repair[38,112]; rotator cuff tears[113–115]; skin ulcers[116,117]; acne scarring[118]; and limb amputation.[119–121]

PRP and Bone Regeneration

PRP accelerates and expands cells' wound healing response and acts biochemically to set the rate and amount of regeneration in bone. Within 10 days, its activity is complete, but this short action has long-lasting effects. For example, the alpha granules in platelets degranulate within several minutes of clot formation, and within 1 hour 90% of their growth factors are released, stimulating osteoprogenitor, endothelial, and mesenchymal stem cells. A graft-surrounding matrix is formed by fibrin, fibronectin, and vitronectin. PDGFs have a mitogenic effect on osteoblast, endothelial, and mesenchymal stem cells. The latter are also acted upon mitogenetically and angiogenetically by TGF-β isomers, which induce osteoblastic differentiation as well. While capillary ingrowth is promoted by VEGF, the lack of epithelial cells renders EGF inert (Fig 1-13a). Within about 72 hours, osteoprogenitor cell mitosis begins and capillary buds appear (Fig 1-13b). In the entire first phase of bone graft healing (about 2½ to 3 weeks), the graft is penetrated by capillaries, and osteoprogenitor cells have greatly proliferated (Fig 1-13c). During this phase, cell instability and infection are common, with the potential for lysing and arresting the development of wound healing. Obviously, prevention of infection and contamination are essential, as is graft stability.[1]

The hypoxic and acidic atmosphere of the wound itself attracts the circulating macrophage and blood monocyte (soon a wound macrophage), both of which assist bone regeneration via the secretion of more growth factors. The clot now contains fibrin, fibronectin, and vitronectin, acting as a matrix for the ingrowth of blood vessels as well as the proliferation and migration of cells. Between 3 and 6 weeks, the proliferation and differentiation of osteoprogenitor cells in the matrix produce osteoid (Fig 1-14), which signals the next (second) phase of healing, when graft and bone join and when adventitial cells develop to support the vascular ingrowth (Fig 1-15). Hypoxia diminishes due to the oxygen provided by the increased blood flow, preventing hyperplasia. By week 6, osteoclasts resorb the osteoid, releasing BMPs and IGF factors 1 and 2, causing the differentiation of nearby osteoblasts and mesenchymal stem cells for maturing bone replacement (Fig 1-16). Mineralized dense bone thus becomes the normal formation now, in the third phase

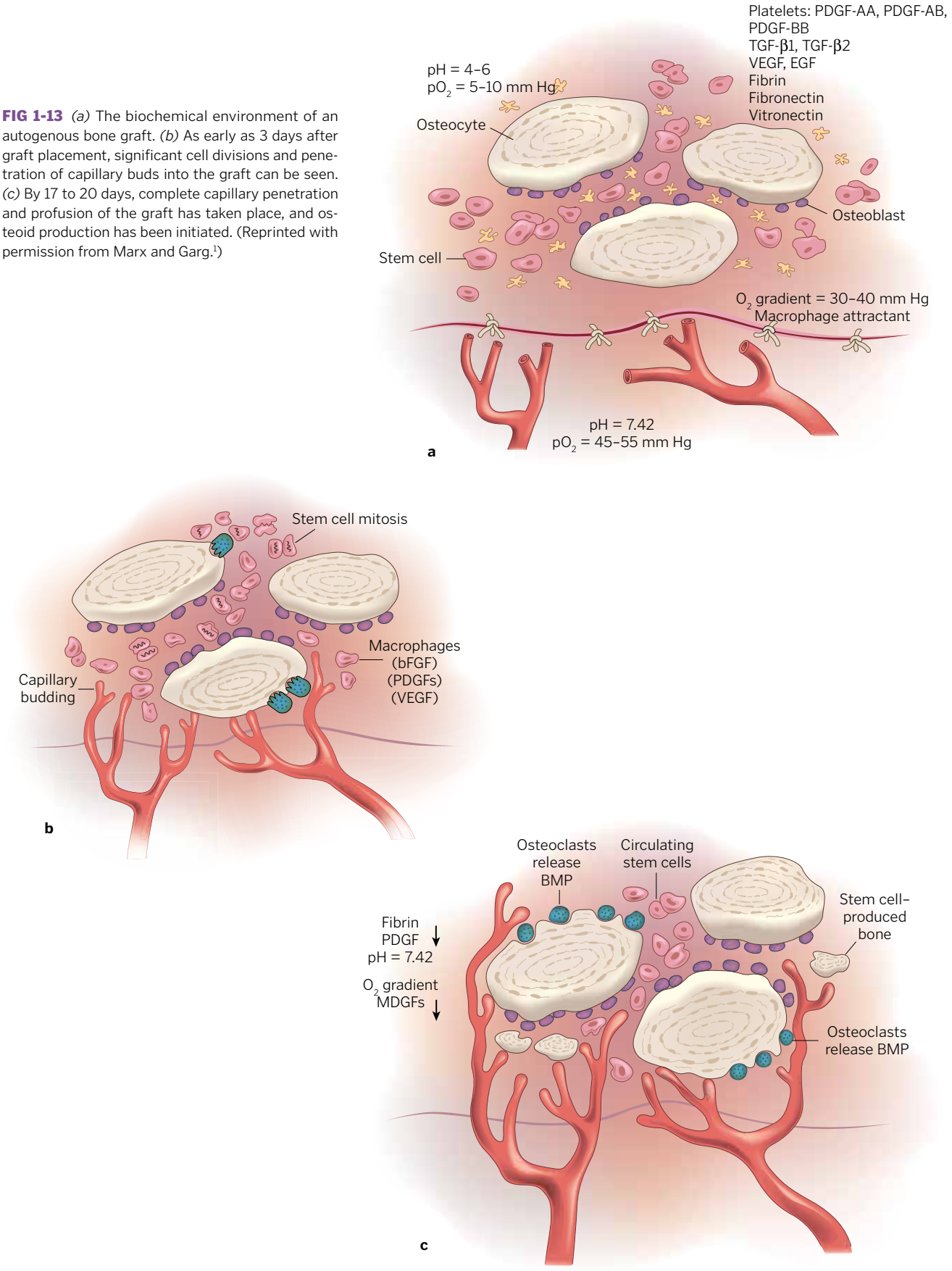

FIG 1-13 *(a)* The biochemical environment of an autogenous bone graft. *(b)* As early as 3 days after graft placement, significant cell divisions and penetration of capillary buds into the graft can be seen. *(c)* By 17 to 20 days, complete capillary penetration and profusion of the graft has taken place, and osteoid production has been initiated. (Reprinted with permission from Marx and Garg.[1])

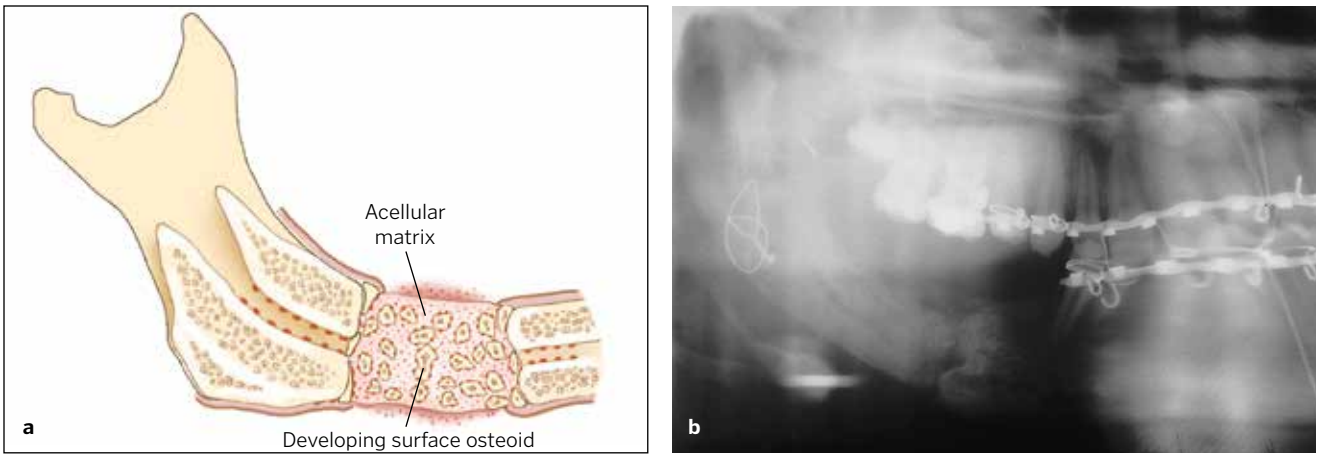

FIG 1-14 *(a)* Acellular matrix along with surface osteoid developing on the endosteal surfaces of the transplanted bone and the resection edges of the host bone in a 3-week autogenous bone graft. *(b)* Corresponding radiograph shows a not-yet-mineralized graft with a "cloudy" appearance indicative of a graft that is not yet consolidated. The radiolucent line between the graft and host bone is the result of a dying-back resorption of the host bone from periosteal reflection. (Reprinted with permission from Marx and Garg.[1])

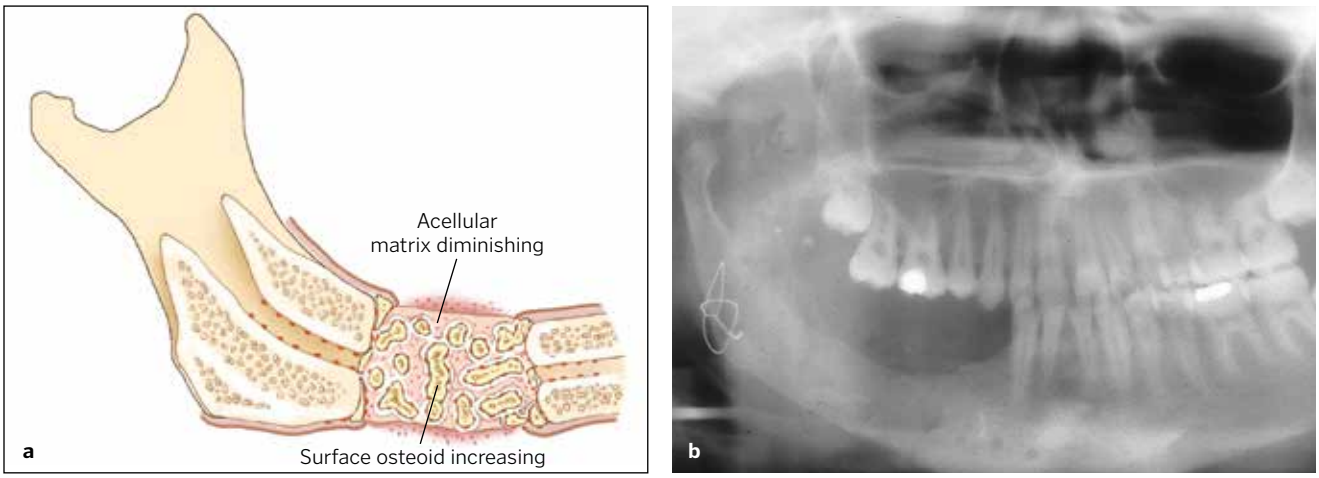

FIG 1-15 *(a)* By fusing graft particles together and to the host bone, the graft has produced sufficient osteoid to consolidate by 6 weeks. *(b)* Corresponding radiograph shows condensation of the cloudy graft appearance, indicative of osteoid production and graft organization. The radiolucent line between the graft and host bone has nearly disappeared as a result of osteoconduction between the graft and host bone edge. (Reprinted with permission from Marx and Garg.[1])

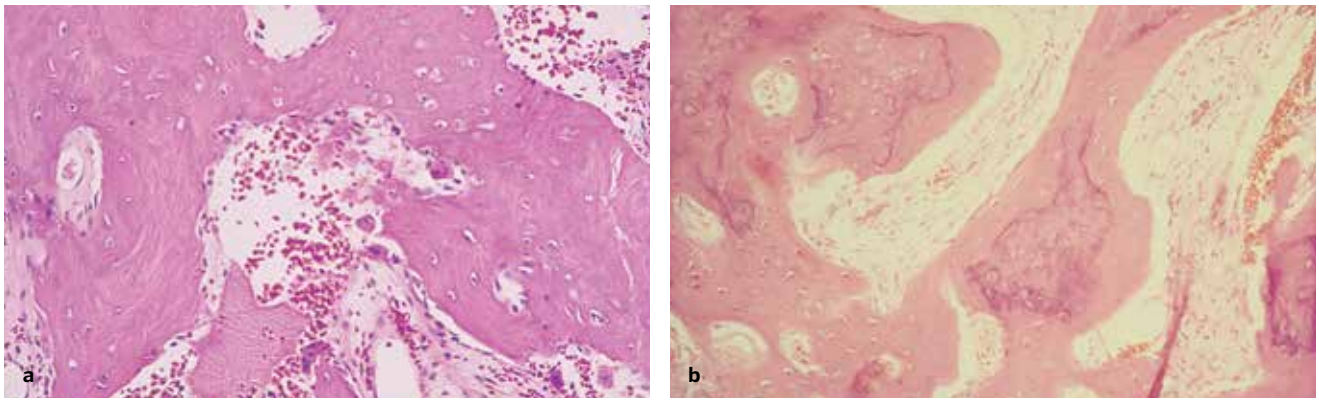

FIG 1-16 *(a and b)* At about 6 weeks, the graft begins a major resorption-remodeling cycle in which osteoclasts resorb the disorganized immature bone and release BMP and insulinlike growth factors, thus inducing formation of new bone that will mature during function. (Reprinted with permission from Marx and Garg.[1])