FRACTURE TREATMENT AND HEALING

HEPPENSTALL

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edited by

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Preface

I first entertained the idea for a new fracture text in 1974. At that time no reference text combining basic research and clinical management of the fracture patient was available for the student or the practicing orthopedic surgeon. It is difficult to envision how a practitioner can provide excellence in patient management without a solid understanding of the basic aspects of the healing process. Only within the last decade has research at both a cell and a tissue level provided us with exciting and clinically applicable insights into the healing process. With this in mind, I approached Jack Hanley at the W. B. Saunders Company to discuss the need for a new fracture text. Mr. Hanley agreed that the concept of a text incorporating basic new scientific and clinical findings into the management of patients with fractures would be a useful addition to the medical literature. At times the task appeared almost impossible to combine with a busy clinical practice. My family was always patient and understanding, which provided me with the motivation to continue through many "wee hours" of the morning.

As with any project, many people played key roles in its production. I will be forever grateful to my training chief, Dr. Edgar Lee Ralston, for his guiding hand and stable influence during and following my training years. He also has a specific interest in fractures, and I am sure that much of his enthusiasm has rubbed off on me through the years. During his time as Chairman at the University of Pennsylvania, he always considered the students and residents as part of his family, providing a very friendly and productive working environment.

Following formal training, I was involved in basic research in the wound healing laboratory of Dr. Thomas K. Hunt. This offered an unusual opportunity to apply soft-tissue research techniques to the fracture healing process, with several interesting results. Dr. Hunt has remained a personal friend and has continued to be extremely helpful through the years. The first chapter of this book was written by Dr. Hunt and is an important contribution, as soft tissue plays a vital role in the fracture healing process.

Dr. Carl T. Brighton, the current Chairman at Penn, has continued to play the most vital role in developing my career. During my training period he guided me through several productive research projects, and we have continued this close relationship. It was through his efforts that I was appointed the Chief of the Fracture Service at Penn. He has written a chapter for the book dealing with the exciting new development of stimulating fracture healing through the use of electrical current.

To my many other co-authors I extend my personal gratitude. Mary Jo Larson provided the many medical illustrations and Karl Ott the photography for the book. Marie Tschantz and Frances Hickman provided the secretarial help and many hours of devoted typing. The valuable assistance of Susan Hunter, Ruth Barker, and Constance Burton of the W. B. Saunders Company is greatly appreciated.

I have attempted to integrate the new basic science and clinical aspects of fracture healing into this text, with the goal of providing a useful reference for students, residents, and practicing orthopedic surgeons. I hope this has been accomplished.

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and

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Wound Healing — 1

Repair is a normal reaction to injury and may be the key to prolonged life in a hostile environment. It is the keystone on which surgery is founded. Despite the lessons of surgical history, it seems that most surgeons accept it as an inevitability, a process that will or will not occur, and having occurred will be "normal"—a single immutable sequence. A look at surgical history reveals, however, that a number of our most fundamental advances have coincided with sudden new insights into the reparative mechanisms. Witness Lister's struggle to separate the fact of sepsis from the fact of normal repair. It has been recognized since the time of Hippocrates that union of two cut edges of tissue can occur without inflammation or sepsis. Yet up to a century ago such an event was so unpredictable that surgeons "incorporated" sepsis into their concepts of normal repair; when "laudable pus"[1] appeared, eventual recovery was expected. When cleanliness had become an ideal, and the microbial theory had become a fact, the stage was set for Semmelweis, Lister, and others to achieve a concept so important that it literally made modern surgery possible. They realized that sepsis and repair were separate phenomena. They learned to expect repair without infection.

Refinements in aseptic technique, the introduction of antibiotics, and improvements in surgical technique, now make primary repair by far the rule rather than the exception. Today the argument would seem to have been won—but has it? In fact, we disagree only in quantity with the surgeons of Lister's early days. Sepsis and delayed union of wounds are no longer considered inevitable; we merely expect them part of the time. Scarring is considered controllable in some—but certainly not all—cases. Repair is not simply the surgeon's ally; it is his concern, his lifeline. Unless the surgeon arranges his priorities to aid the forces of repair and to mobilize resistance to infection, he will be, in substance, little more than a surgeon of the last century who somehow has found a modern operating room.

INJURY

When tissue is injured, blood vessels are broken or cut. Platelets bind to the exposed collagen and release their phospholipids, which stimulate the intrinsic coagulation mechanism. Injured tissue cells release thromboplastin, which activates the extrinsic coagulation mechanism. At the same time, the aggregating platelets, and perhaps white cells, release proteolytic enzymes that initiate the cascade of proteolytic enzymes in the complement system. As this enzymatic cascade rapidly amplifies the distress signals of injured tissue, chemotactic substances accumulate and call forth the inflammatory cells, which are first seen sticking to the sensitized endothelial membranes of local vessels. The cells follow the chemical signals to the area of injury and bind their membranes to the various components of injured tissue. The

phagocytic cells ingest these altered substances, and the act of phagocytosis "activates" them.

Exactly what calls forth the sudden burst of fibroblast replication near the area of injury is unknown. The evidence suggests that platelets activated by thrombin and macrophages activated by phagocytosis release a substance or substances that can stimulate replication of fibroblasts. No matter what the signal, the evidence is clear that the vast majority of the total fibroblast population originates in the wound itself, probably stemming from cells located in or around local small vessels.

Fibroblasts in cell culture do not necessarily make collagen. It seems necessary to stimulate them to do so. The most prominent stimulators of collagen synthesis in cultured fibroblasts are ascorbic acid and lactate ion, which "activate" enzymes necessary for collagen synthesis. The lactate that accumulates after several hours of hypoxia will also "activate" these enzymes. The hypoxia or the concentrations of ascorbate and lactate necessary to stimulate collagen synthesis in cell culture are actually present in wounded tissue. As the numerous cells that are called into the wound reach the environment of damaged vasculature and limited oxygen supply, anaerobic metabolism inevitably results. The extracellular oxygen tension in this area falls well below 10 mm Hg, a point probably below the critical or lowest optimum level for aerobic metabolism in both fibroblasts and leukocytes. Possibly for this reason, fibroblasts and new epithelial cells start their lives with a prominent capacity for anaerobic metabolism. The by-product of the glycolytic pathway of anaerobic metabolism is lactate. Furthermore, leukocytes and macrophages, when "activated" by the ingestion of altered substances or foreign body, have a prodigious capacity for lactate production in either aerobic or anaerobic conditions. Within a few days, lactate in the extracellular fluid of the central dead space of wounds is in the region of 10 to 15 millimolar.

THE WOUND MODULE

At this relatively adult stage, the wound cells form a rather vague "module of repair" (Fig. 1–1). In the van of the advancing wound edge is the macrophage. Wound macrophages seem to be chronically activated and are usually found with ingested substances in their digestive vacuoles. Just behind these cells are some maturing but still youthful fibroblasts, apparently the products of nearby cells that are actively dividing. Cells undergoing mitosis are normally found between the first functioning capillary and the first maturing fibroblast of the wound edge. The most distal functioning blood vessel is stationed just behind the first maturing fibroblasts. It sprouts new capillary buds that are destined to complete an arcuate path through the injured tissue, either to unite with a vessel from the other side in primary repair,* to unite with a cut vessel end in a skin graft, or to join another similar bud from a lower or higher pressure point in the granulation tissue of an open or dead space wound.† The new and tender microcirculatory loops find external support in the collagen gel secreted by the immature fibroblasts. Without such support they would inevitably rupture as soon as they were exposed to the pressure of the arterial system. As each new capillary loop becomes functional, more oxygen becomes available to the cells of the wound "module." The fibroblasts, now in a higher oxygen pressure, can synthesize more collagen and can migrate further until they again run out of oxygen. The process continues in a cyclic fashion. As the "module" proceeds, the collagen-synthesizing fibroblasts are left behind to continue their work of constructing and reconstructing the new connective tissue.

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*"Primary repair" is the term used to describe healing of a wound that is accurately reapproximated and mends with minimal space between its edges. It is sometimes called repair by first intention. Closure of a wound on the fourth or fifth day is often called delayed primary closure.

†Healing of a dead space or open wound is said to occur by second intention. It involves filling of a tissue defect through formation of large amounts of new connective tissue, new vessels, and new epithelium in many cases. The term usually implies an external, open wound, but the repair involved is much the same as in healing of a closed space such as a pneumonectomy space, or a serum or blood collection such as often occurs in fractures.

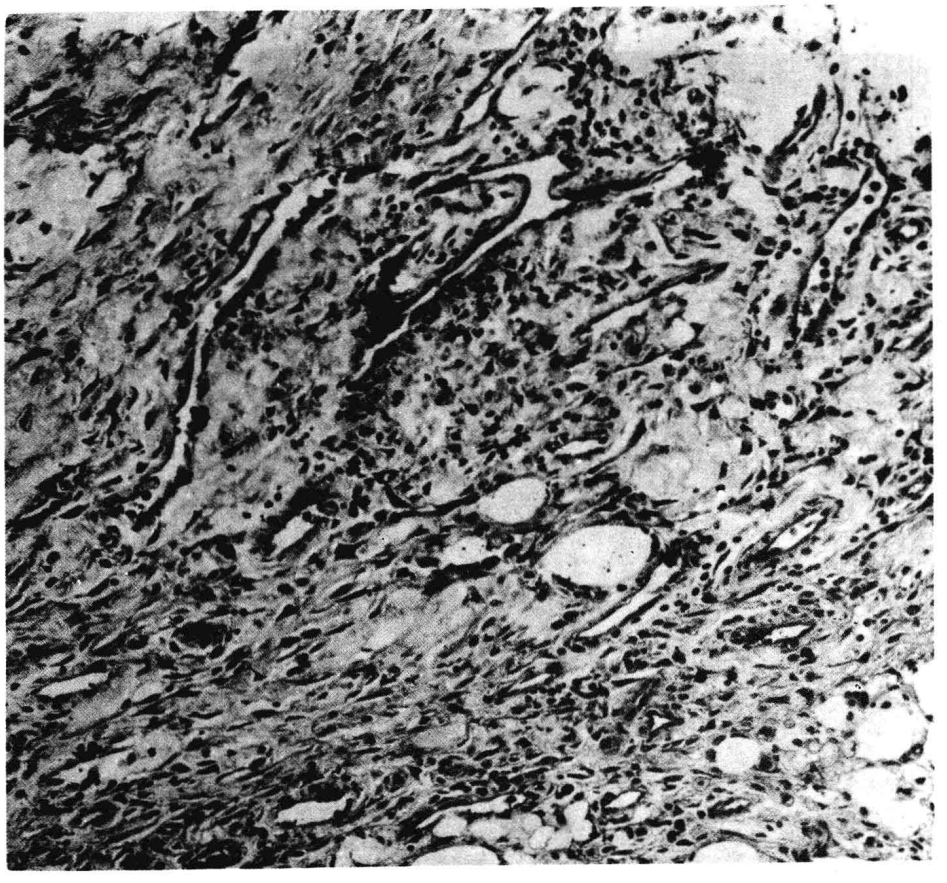

Figure 1–1 Medium-high-power magnification of granulation tissue from a "dead wound" in a rabbit. The central space of the wound is in the upper right corner. All this tissue is new. Small vessels can be seen emptying into the dead space. Macrophages can be seen on the surface, and fibroblasts are scattered about below. Some remodeling of the fibrous tissue into fat is seen in the right lower corner. Reprinted from Fundamentals of Wound Management in Surgery, Chirurgecon, Plainfield, N.J.

The concept of the advancing "module" implies that there are metabolic gradients in the wound that probably influence its form and its motion. One would expect that, if the foregoing description is accurate, there would be a very low oxygen tension at the surface of the macrophage in the wound module. In fact, this is true. Measurements of oxygen gradients show that the P_{O_2}, which is in the region of 50 mm Hg over the arteriolar portion of the capillary, falls to near 0 mm Hg at the surface of the macrophages and in the dead space. The lactate, hydrogen ion, and P_{CO_2} gradients slope in the other direction—that is, high in the dead space and lower near the functioning vessels.

LEUKOCYTES—THE MACROPHAGE

Leukocytes appear in the wound within a few hours. At first, they are mostly polymorphonuclear cells, but by about the fifth day the predominant leukocytes are macrophages. This type of cell remains in the wound until it is healed (Fig. 1–2).

Primary repair occurs uninhibited even by major reductions in the numbers of circulating and tissue neutrophils and lymphocytes in the system. Their role is to inhibit and kill contaminating bacteria. When the macrophage is eliminated from the healing wound, however, even primary repair suffers. Macrophages are wandering mononuclear cells found in tissues and

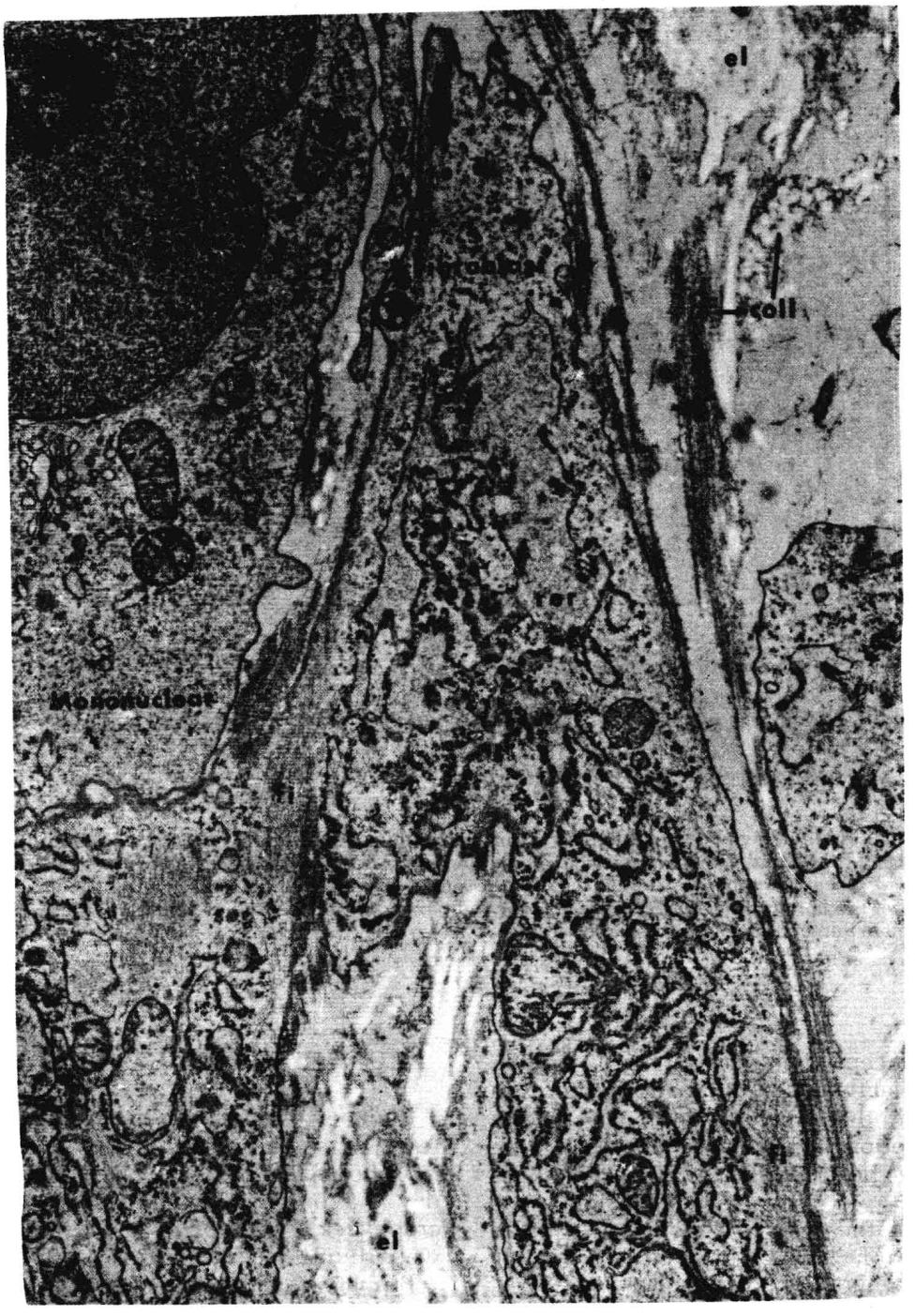

Figure 1–2 Electron microscope view of one field in a wound, demonstrating the intimate relationship between mononuclear cells and fibroblasts. There are a few filaments in the periphery of the fibroblasts, suggesting that there might be some smooth muscle function in the cell. A layer of extracellular collagen (coll) can be seen around the fibroblasts. *el*, elastin; *fi*, fibrin; *rer*, rough endoplasmic reticulum. (Courtesy of Russell Ross, Ph.D., University of Washington Medical School). Magnification × 17,000. Reprinted from Fundamentals of Wound Management in Surgery, Chirurgecon, Plainfield, N.J.

tissue spaces. They are actively phagocytic and can kill organisms in a manner apparently similar to that of polymorphs. They can ingest particles and macromolecules, and excrete the products of digestion into the surrounding environment. Recent laboratory research suggests that local macrophages can play a nutritional role by acting as "the digestive tract of the wound." Probably most important, however, is that macrophages seem to act as director cells. The case is strong that the macrophage is the key cell of the inflammatory response to injury. It (1) debrides injured tissue, (2) processes macromolecules to useful amino acids and sugars, (3) attracts more macrophages, (4) probably signals for fibroblast replication, (5) may signal for neovascularization, and (6) secretes lactate.

In some unknown manner, vitamin A aids the entrance of macrophages into the wound. This important vitamin is vital to the initiation of repair. If macrophage entry is prevented by antiinflammatory steroids, repair can usually be stimulated by giving vitamin A. In this case, the vitamin A administration is followed by increased leukocyte and macrophage entry into the wound.

VASCULAR ENDOTHELIUM

One of the most important and least appreciated aspects of repair is the regeneration of new blood vessels. Neovascularization is seen in injuries, infarcts, areas of inflammation (especially those attended by certain types of macrophagic inflammation), and tumors. The function of angiogenesis or neovascularization in wounds is to nourish tissue that obviously cannot be well nourished unless new vessels can replace and supplement the old, injured system. Present concepts rest on two major facts: First, new vessels originate from existing vessels; and second, whatever their ultimate size or function becomes, all new vessels begin as capillaries (Figs. 1–3, 1–4, 1–5, and 1–6).

The new vasculature is formed, in general, in three ways. The first is by generation of a whole new vascular network where a large tissue defect has to be filled. The second is by union with an unused network as the host bed provides circulation to a skin graft. The third is by joining (or rejoining) of vessels across a primarily closed wound.

It seems most instructive to consider the generation of a new vascular network first.

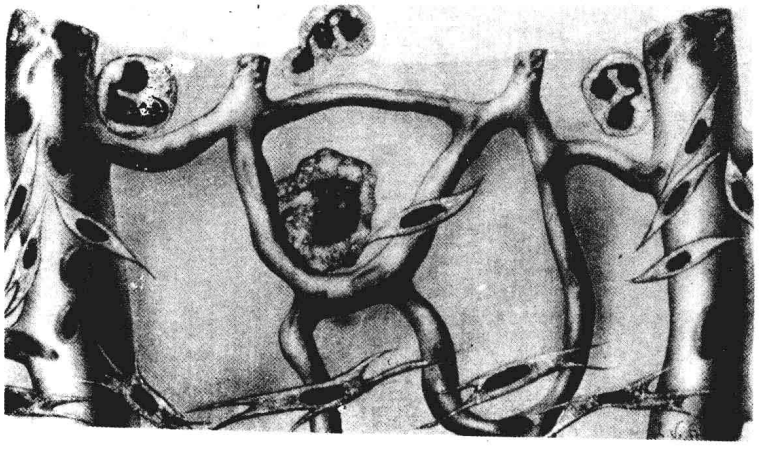

Figure 1–3 Schematic drawing of the wound just after injury. Vessels have become thrombosed with platelet and fibrin clots, and an early inflammatory exudate is appearing. This and the following series reprinted from Fundamentals of Wound Management in Surgery, Chirurgecon, Plainfield, N.J.

Figure 1–4 This wound, at five to seven days, now shows an inflammatory exudate dominated by mononuclear cells. Fibroblasts have appeared, mostly from their usual origin in perivascular cells. Endothelial capillary buds are present in the center of the preexisting capillary arcade.

The clinical circumstance is healing of a dead space in tissue—a severe fracture, for instance. First, the injured vessels become thrombosed. The wound module is assembled, and from the functioning vessels nearest the wound, sprouts of vascular cells appear from the bases of the existing endothelial cells. Such capillary sprouts are pictured in Figures 1–4, 1–5, and 1–6. These new vessels somehow join with similar sprouts from a lower or higher pressure system to form a functioning capillary loop. Later on, this loop will either participate in formation of a larger vessel or

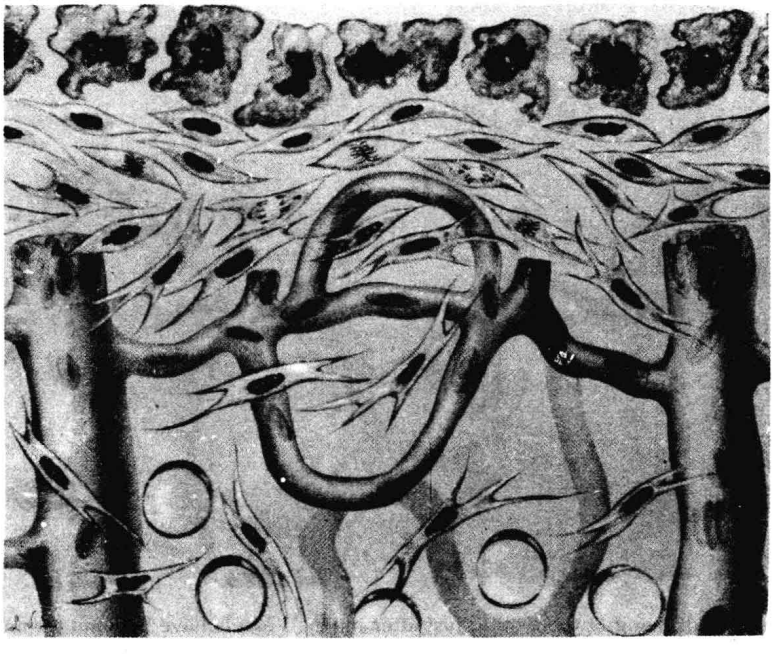

Figure 1–5 At about 10 days the fibroblast response is at its peak. The "wound module" is complete. There is a new functioning capillary loop in the center.

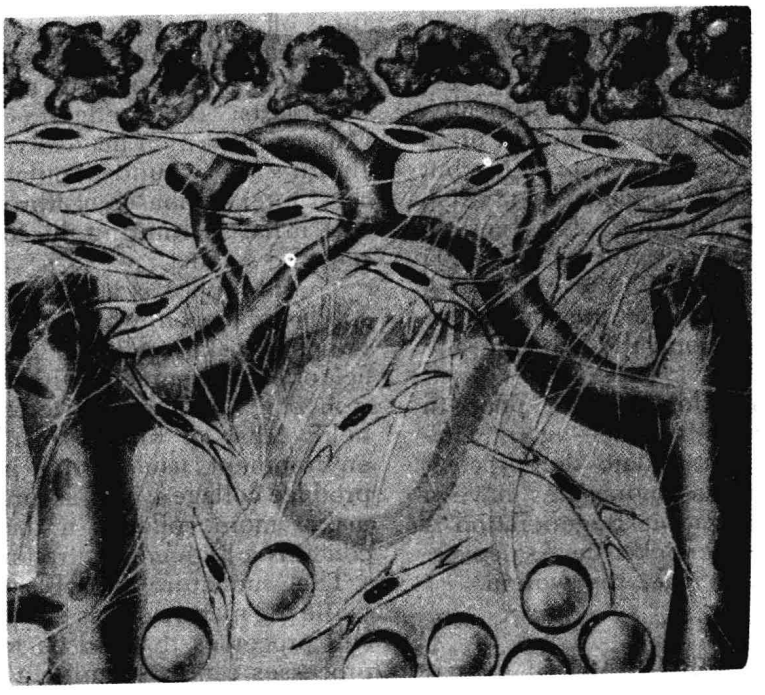

Figure 1–6 The edge of the wound has advanced. More capillary loops have formed and some old loops have dropped out or become "ghost vessels." The supplying artery and vein are becoming larger and larger because they are now supplying an increased volume of tissue. Compare these with Figure 1–19, which shows much the same section in a real wound.

will stop functioning and disappear.

Some vascular sprouts appear to have no lumina. Others appear to be open-ended tubes through which red cells escape. This last type would seem to predominate in primary repair or revascularization of a skin graft. For a while after cannulation has occurred, the new endothelial cells fit loosely and the new vessels are fragile and "leaky." Large particles in blood, colloidal carbon for instance, leak between the cell junctions and are phagocytized by macrophages, perhaps "activating" them. There is no ready explanation for the stimulation for new vessel formation. The molecular signals are entirely unknown, though as noted, macrophages and platelets seem to have the capacity to make the signals. We have seen new veins 2 or 3 mm in diameter traversing the space across totally enclosed wire mesh cylinders. Arteries up to 1 mm or more in diameter have been seen in ear chambers. Vascular studies on healing tissues have shown that arteries up to 3 mm have regained continuity across the base of a pedicle flap. One can only speculate that, somehow, hypoxia plays a role. The loss of a metabolic stimulant to new circulation would seem to be adequate explanation for lack of flow within vessels, thus explaining the gradual disappearance of unused vessels after healing is complete. Exactly how the stem vessels become larger and larger as more and more tissue has to be traversed and more and more tissue is supplied, is, as yet, an unsolved mystery.

In primary repair, reestablished circulation bridging the wound can be noted by the second or third day. The manner in which reconnection of vessels occurs is not understood. It seems likely, however, that thrombosed vessels may be reopened by the thrombolytic mechanism. Most vessel endothelia contain fibrinolysin, which may open "holes" in the fibrin that initially locks the wound edges together. Pathways for blood cells may form thereafter, just as oft-walked paths in a field become worn by constant use. Such a pathway would be an ideal guide for sprouting endothelial cells.

Vascular regeneration is, as one might expect, a delicate process: Excessive mo-

tion can destroy it. Histamine depletion and numerous of the cytoplasmic poisons used in chemotherapy stop it. Vascular regeneration is poor in tissue bearing chronic changes of radiation exposure. Clinically, however, we find that the placement of an autograft or heterograft on viable but wounded and radiation-damaged tissue, followed by administration of oxygen to maintain the arterial P_{O_2} in the region of 200 mm Hg, is followed by obvious evidence of neovascularization hitherto unseen in the wound in these chronically scarred and wounded tissues.

Vascular regeneration is also poor in steroid-treated patients. Once again, vitamin A seems to restimulate the process, further indication that monocytes have a role in neovascularization. Regeneration is also inhibited in ischemic tissue. As neovascularization goes, so goes the wound.

THE FIBROBLAST

The fibroblast synthesizes and deposits collagen and proteoglycans. There has been controversy about the site of origin of fibroblasts. The basic reason for the controversy has been that the fibroblast, as seen in the actively healing wound, is not seen in normal tissue. Since fibroblasts are rare in tissue, they were once thought to be derived from blood spilled into the injury. Extremely sophisticated experiments with symbiotic animals, however, with radiation inhibition of cells in wounded tissue, give the irrefutable answer that all or almost all fibroblasts found in the wound originate in the injured tissue. Most of the cells appear to rise from perivascular cells. Whatever the signal, the response is extraordinary—especially in connective tissue in which a relatively acellular tissue is converted to one that is almost pure cells within a few days.

The mature fibroblast is pictured in Figure 1–2 and diagrammed in Figure 1–7. It is richly endowed with endoplasmic reticulum, Golgi apparatus, and mitochondria, as are other protein-synthesizing cells. It is mobile and migrates in tissue culture. Its mobility is subject to contact inhibition, leading some to say that the contact of the fibroblasts of one side of a wound with the fibroblasts of the other is the signal that turns off repair. Unfortunately, this concept does not stand even first examination, since the object of repair is not edge-to-edge fibroblasts. It is edge-to-edge collagen. Contact inhibition may serve as a means of limiting the wound population during the most intense phases of fibroplasia, but any role it has in limiting the totality of repair must be small.

The fibroblast is a hardy cell. It favors a solid surface on which to attach and migrate. It makes collagen best in a slightly acidotic environment with an oxygen tension of over about 10 to 20 mm Hg but below that of air. It needs a reducing environment, usually rich in ascorbate, to produce collagen; and, as outlined earlier, it makes more collagen if that environment contains a high concentration of lactate.

The immature fibroblast is rounded, while the mature one is elongated with long cell processes that aid its mobility. These processes can even guide a fibroblast over or under a nearby fibroblast. Some fibroblasts have a rich supply of myofibrils and appear to be a hybrid "myofibroblast." This cell will contract and relax in response to the usual stimuli. Such cells are found in contracting wounds, where they seem to furnish at least part of the contractile force. They are also seen in large arteries, where they participate in the process of arteriosclerosis.

In view of modern genetic theory, it seems possible that almost any mesenchymal cell could become a fibroblast. Almost every animal organism ever analyzed contains collagen-proteoglycans or chitin-proteoglycans. The genetic code for collagen synthesis would seem to be present in most vertebrate cells; in fact, even some epithelial cells have been induced to produce collagen.

The fibroblast has a full complement of metabolic pathways. It synthesizes collagen, of course, but also synthesizes proteoglycans and elastin. It can synthesize cholesterol and the like. It respires and makes its own adenosine triphosphate. Thus, its requirements probably include most of the B vitamins as well as ascorbate, oxygen, amino acids, and trace metals such as zinc, iron, and copper. Metabolic needs are met by circulating sugars, fats, amino

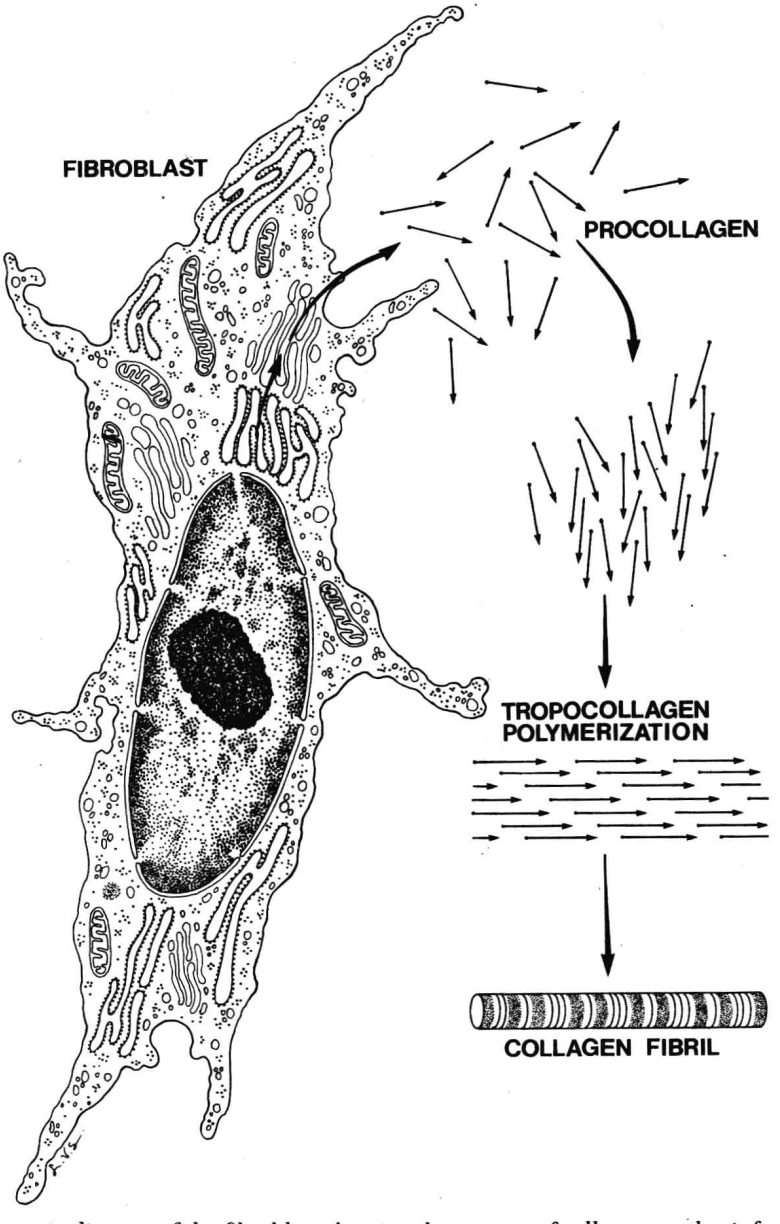

Figure 1–7 Schematic diagram of the fibroblast showing the process of collagen synthesis from the endoplasmic reticulum, through the Golgi apparatus, to the extracellular space in the monomer form, and then polymerization of the monomer into collagen fibrils. Reprinted Courtesy of Chirurgecon, Plainfield, N.J.

acids, oxygen, ascorbate, and similar substances. The macrophage may break down local large molecules into reusable amino acids for fibroblast use. Lastly, the fibroblast itself is pinocytic and may supply some of its glucose and amino acid requirement through hydrolysis of more complex molecules.

COLLAGEN

Collagen is the principal structural protein of the body and the major constituent of skin, tendons, ligaments, bones, cartilage, fascia, and the septa of various organs. Of more importance to wound healing, it is the principal component of scar tissue and the

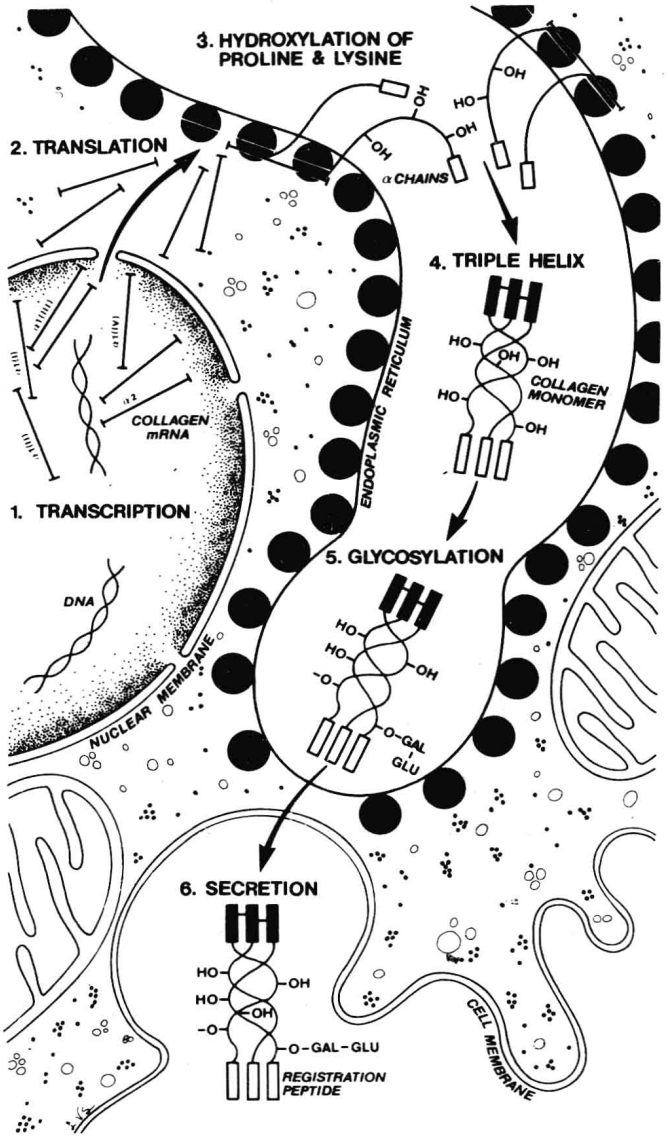

Figure 1–8 Highly diagramatic representation of the steps in collagen synthesis from translation to secretion. The collagen monomer seems to be excreted into the Golgi apparatus, where glycosylation occurs. The molecule is excreted from the cell with the registration peptides still in place. The registration peptides must be cleaved before further polymerization and fibril formation can occur normally. Reprinted Courtesy of Chirurgecon, Plainfield, N.J.

principal product of fibroblasts (Fig. 1–8). It has many chemical and structural properties to distinguish it clearly from other proteins.

When we use the word "collagen" we now mean not a single substance but a group of glycoproteins that have the following attributes in common:

1. They are composed of three separate linear peptide chains of approximately equal length, each containing about 1000 amino acids. These are alpha chains. Each chain is made up of one third glycine, one third proline and hydroxyproline, and one third other amino acids. Glycine occurs in every third position, making a repeating structure of glycine-X-Y. X and Y may be any amino acid, but hydroxyproline and hydroxylysine are usually found in the Y position.