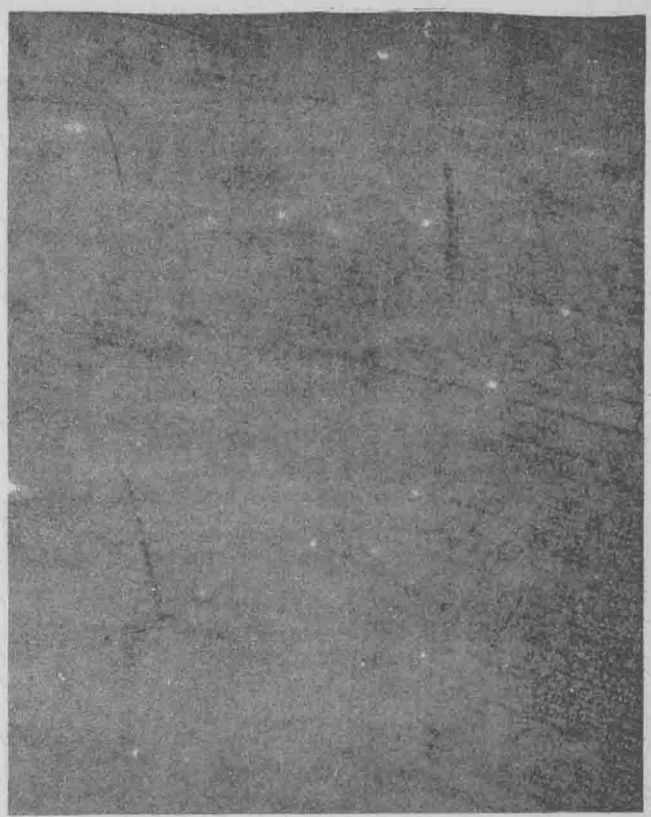
SURGICAL PHYSIOLOGY

BURKE



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Preface

There is an art and a science of surgery that complement each other, and when used together they provide a patient with a treatment that is most likely to succeed and least likely to cause harm. Although the science of surgery is a relative newcomer compared to the practice of doing, its importance has been accelerated by the explosion of biologic information largely generated by support of biomedical investigations by the National Institutes of Health following World War II. This increase in knowledge has provided thoughtful guidance of the surgeon's hand through a broad base of available, previously acquired knowledge. To provide acceptable surgical treatment it is no longer sufficient to simply possess superior dexterity and extensive, though narrow, experience in operative technique which, although important, do not make a master surgeon. Present resources now require that surgical practice be guided by an intimate knowledge of the physiologic principles involved. This present volume attempts to coordinate the science with the art of surgery to ensure maximal treatment benefit.

In our attempt to provide a text of relevant physiology, we have concentrated on areas that directly apply to the practice of surgery. The book is designed to provide an explanation of the physiologic principles that govern surgical practice with recognition that the surgeon must be an applied physiologist. Human physiology provides a framework within which treatment must be designed if the best therapeutic success is to be achieved. In this sense, physiology forms the logic of surgical treatment. In order both to understand why surgical procedures are designed as they are and to choose the most effective operation in a given circumstance, normal physiology must be clearly understood. It is not the purpose of this book to provide a complete text of human physiology, but rather to provide a text limited to those areas of physiology that are directly important to an understanding of the character and appropriate application of surgical treatment of disease. The book therefore includes chapters concerning metabolism, defense against infection, respiration, cardiovascular, renal, and gastrointestinal function, as well as pertinent immunologic and neuroendocrine sections. In this way the book should act as a codicil to texts and atlases of technical surgery. The work is designed to act as a reference for the practitioner and as a text of physiology supporting the clinical education of surgeons in training.

JOHN F. BURKE

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Chapter 1

Physiology of Wound Healing

by

Thomas K. Hunt, M.D.

The idea of "physiology of wound healing" was unthinkable just 5 to 10 years ago when the measurements of healing then available could measure, at best, only changes that developed over a period of days or weeks rather than minutes or hours. However, in the past few years advances in monitoring techniques and biochemical methods have made it possible to measure the effects on repair of rapidly moving changes in body physiology. These methods have shown that healing is affected—often dramatically—by systemic physiologic changes. This information has forced us to accept new explanations for old observations, and new clinical methods of management of wounds have resulted. For instance, whereas the cause of abdominal dehiscence was once attributed solely to distention and cough, it has now been traced to disorders of blood flow, pulmonary function, and nutrition. Similarly, the etiology of wound infection no longer is attributed simply to wounding and contamination. We know that the battle between host defenses and bacteria, which is fought in *every* wound, is profoundly affected by ischemia, hypoxia, hypovolemia, coagulopathies, and other such events.

WOUND BLOOD SUPPLY

The central point at which physiologic changes occur in a wound is its three vascular supplies—the one it starts with, the one the surgeon leaves it, and the one that regenerates during the healing process. Tissue that is ischemic to begin with heals poorly and is easily infected. Highly vascular tissues, such as the faces of children, heal in a few days and are almost uninfectable.

When tissue is injured, vessels are injured. More vessels suffer in a tearing, avulsing wound than in a clean-cut one, and more in a clean-cut one than in a needle penetration. Also, the degree of systemic injury affects wound blood supply. The more tissue injury there is, the more blood loss, the greater the consumption of coagulation factors, the greater the endocrine response, the greater the increase in blood viscosity, and so forth. Whether the injury is local or diffuse, the greater the injury, the poorer the wound blood supply and consequently the more difficulty the wound encounters in its healing. The greater the injury, the greater the physiologic disturbance, the less well each wound heals.

Injury, Thrombosis, Inflammation, and Angiogenesis. At the moment of injury, vessels contract and the blood in them coagulates. Coagulation and complement factors interact and both systems contribute to the inflammatory reaction that normally follows. One result of coagulation, complement activation, and ischemia is inflammation, which then becomes a stimulus to fibroblast and endothelial cell proliferation.[3]

When the injured vessels clot, a volume of tissue around the wound is left ischemic. In sharply cut skin and fascial wounds, the ischemic area is 50 to 100 μ wide. Wounds of the face, where intercapillary distances are smaller, have a much smaller ischemic volume. In burn wounds, the volume of ischemia may be vastly larger; it varies according to the temperature and duration of the thermal exchange. Thereafter, the vascular injury deep-

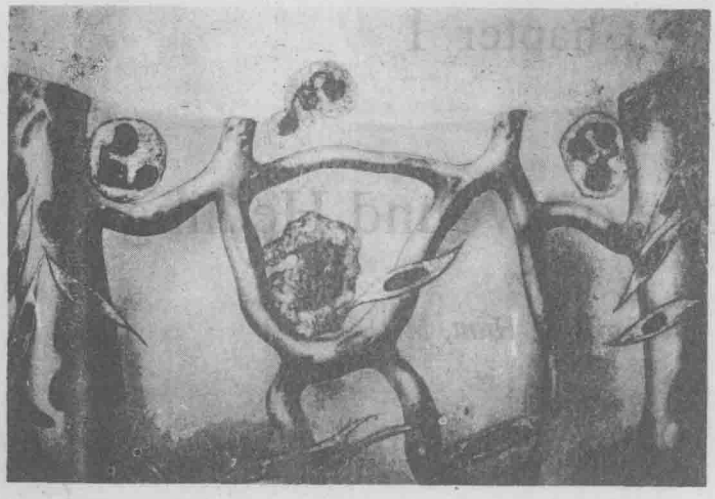

Figure 1–1. Schematic representation of the wound just after injury. Vessels have thrombosed and an inflammatory exudate, mostly polymorphonuclears, is appearing. Serum covers or fills the wound, and serum contains stimulators of cell replication some of which are made by platelets. The avascular area is developing but will not reach its full thickness for several days. Oxygen supply can be increased in the normovolemic patient by raising arterial PO_2 (From Hunt TK, Dunphy JE (eds.). Fundamentals of Wound Management. New York, Appleton-Century-Crofts, 1979.)

ens steadily for about 48 hours, and the end result may be an ischemic area a centimeter or more deep. Avulsed wounds and burns may have an avascular area many times as thick as incised wounds, and the ischemic tissue may need to be removed (debrided) in order to prevent infection and allow healing within a reasonable time.[19, 29]

In an optimally made and primarily closed wound, tissue damage is slight and does not progress. Thrombolysis is active, and some vessels at the wound edges will reopen and connect with vessels on the other side of the wound as soon as 3 to 5 days after injury. Skin grafts depend heavily on this process for survival and healing. Of course, new collagen supports these fragile junctions between vessels.[19, 26]

Open or dead space wounds depend on generation of new tissue and vessels for nutrition. This "angiogenesis" or "neovascularization" is absolutely necessary. The source of the angiogenesis is the local vascular tissue, and the signals seem to originate in platelet thromboses through the action of "platelet factor" and from a factor secreted from macrophages. The result is formation of new vessels which then supply nutritional support to youthful fibroblasts and in return receive physical support from the fibroblasts and the collagen they secrete. The new vessels form the core of an ecosystem of cells which is in a sense a "module" of repair. The "module" is made up of: (1) the new blood vessel, (2) the fibrous tissue around it, and (3) the macrophages and fibroblasts, which seem to be led

Figure 1–2. The developing "granulation tissue" now shows a more orderly arrangement of inflammatory response which is now predominantly macrophagic. Fibroblasts have appeared—mostly from perivascular cells; their mitoses are seen near the distal-most functioning vessels. Endothelial capillary buds have appeared. PO_2 is now about 15 mm Hg at the macrophage layer. PCO_2 is 60 to 80 mm Hg, and pH is in the region of 7.2. (From Hunt TK, Dunphy JE (eds.). Fundamentals of Wound Management. New York, Appleton-Century-Crofts, 1979.)

Figure 1–3. A new functioning capillary loop has been found. This "wound module" is complete, but is a granulating wound. New arcades will appear until the space is closed. In primarily closed wounds, the capillary buds will connect across the incision with buds from the other side. The new loop in the center has raised the PO_2 in that area. The new vessel is extremely sensitive to catecholamines. (From Hunt TK, Dunphy JE (eds.). Fundamentals of Wound Management. New York, Appleton-Century-Crofts, 1979.)

by chemical signals originating from macrophages and from blood clot.[13] The module, emphasizing angiogenesis, is depicted in Figures 1–1, 1–2, and 1–3.

THE WOUND ENVIRONMENT

In any wound, fibroblasts will eventually be required to synthesize and accumulate collagen at the point that is farthest from functioning circulation. In normal connective tissue, the circulation is never particularly plentiful. After an injury, much of it is destroyed. Yet, at this point inflammatory cells and fibroblasts will accumulate and will make metabolic demands far beyond the normal for that tissue. Clearly, the injured local blood supply is inadequate for the healing that will follow. An anaerobic environment results. Oxygen tension (human and animal) falls rapidly from the 150 mm Hg of the air left trapped in the wound to about 50 mm Hg in the first 24 hours. In the next 24 hours, it falls to about 30 mm Hg and thereafter into the 20 mm Hg range (Fig. 1–1). If a "dead space" results, PO_2 may fall to almost zero in it.[15, 24]

At the same time, PCO_2 rises. In primarily closed wounds, PCO_2 rises only in small amounts because carbon dioxide is highly diffusable even through the fairly long diffusion distances characteristic of tissue injured by a scalpel. Hydrogen ion concentration falls. In the human, the pH falls from about 7.4 to about 7.2 within the first 48 hours. In dead space wounds, PCO_2 may rise to over 100 mm Hg. The pH may fall to 7.1. Lactate concentration may rise into the hundreds of milligrams per 100 ml or 10 to 30 mM/liter (normal serum lactate equals approximately 1 mM/liter).

These gas tensions, hydrogen ion concentrations, and lactate concentrations reflect a tissue in respiratory distress. It is reasonable to assume that cells cannot reach full "functional capacity" under these conditions. Experiments with animal and human tissues and in individual animal and human fibroblasts have shown that fibroblast "function" is compromised as PO_2 falls and PCO_2 rises. Collagen synthetic capacity fails totally, both in theory and in fact, when extracellular PO_2 falls below about 5 mm Hg, at which point PO_2 at the endoplasmic reticulum probably reaches zero. Similarly, in this environment, it becomes impossible for leukocytes to perform their full range of "functions," although leukocytes in many ways are facultative anaerobes. This will be discussed later. Obviously, local microcirculation must improve before much healing can occur.

As repair proceeds and new vessels form, the environment improves somewhat. In a dead space wound, oxygen tension will rise slowly to the 20 mm Hg range, whereas in *primarily* healing wounds the oxygen tension never falls that low. Furthermore, it begins to

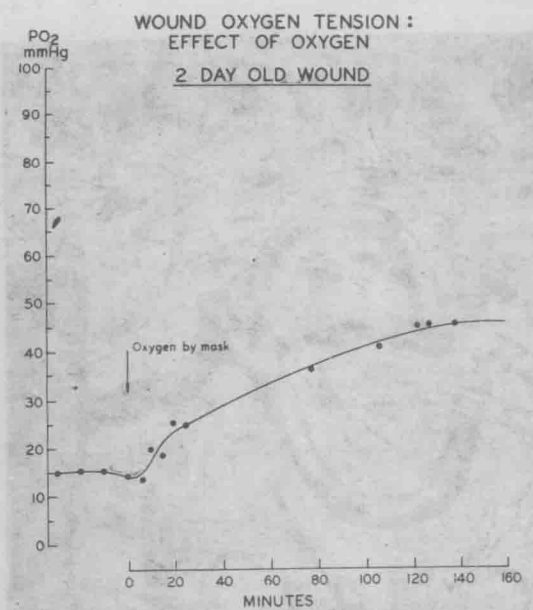

Figure 1–4. The effect of breathing 90 per cent oxygen (arterial PO_2 = 500) on the PO_2 of a wound in a rabbit. The effect developed slowly in this 2-day-old wound, but it became faster as the wound aged.

return back toward normal after about the fourth day when blood vessels begin to connect across the wound space. In human dead space wounds, the hydrogen ion concentration remains about 7.2, the carbon dioxide tension in the region of 60 to 100 mm Hg, and the lactate in the region of 10 mM. The range of values for these substances in primarily healing wounds is not known but they probably reflect the fact that oxygen supply in primarily healing wounds is somewhat better.

Despite all this, one should not gain the impression that the gas tensions and hydrogen ion concentration are totally determined by the location of the wound and by the injury. If the wound is crudely made and contains necrotic tissue, it cannot be brought to life by any means. However, *if the wound has been made with reasonable skill, all these values can be significantly affected by changes in systemic physiology.* For instance, Figure 1–4 shows the range of changes in oxygen tension that can be produced in rabbit ear chamber wounds merely by changing arterial PO_2.

CIRCULATION, OXYGEN, AND FIBROBLASTS

Figure 1–5 demonstrates that wound collagen synthesis is dependent upon oxygen supply. The tests reported in Figure 1–5 were performed in dead space wounds in rabbits. Wire mesh cylinders were placed under the skin, and the rabbits were placed in atmospheres containing 12 per cent oxygen, 20 per cent oxygen (air), and 45 per cent oxygen. Ambient carbon dioxide was kept below 1 per cent.[16] The same relationships have been demonstrated: (1) in tensile strength of primarily closed animal wounds;[31] (2) for collagen production in tissue slices from both animals and humans;[4] and (3) for collagen production in individual fibroblasts isolated from both animals and humans.[7] The only important point in which this relationship has not yet been demonstrated is in some measure of human wound healing in the intact patient. Up to now, no such tests have been possible, but the argument is so strong that one must presume that when such tests are done the oxygen effect will again be demonstrated.

The relationship of the arterial PO_2 to oxygen supply in the wound may not hold in every wounded tissue. It certainly holds in connective tissue, where intercapillary distances are great. It may or may not hold in the highly vascular wounded liver or perhaps even in well vascularized intestine. Tests on animals show that it applies to skin and subcutaneous tissue more than it does to colon. It probably applies less in stomach, where vascularity is rich and diffusion distances are not great even in cut tissue. Obviously, therefore, there are tissues and circumstances in which *hyperoxia* may not profoundly affect repair. However, prolonged *hypoxia* probably is always deleterious. Hypoxia affects even the regeneration of liver,[28] which occurs within the context of a dense capillary vascularity. Furthermore, arterial hypoxia is probably always important to injured tissue even when the acute compensatory mechanisms (such as hemoglobin-oxygen affinity changes) are operative.

The mechanisms by which oxygen supply influences repair are not fully clear. Early in the history of a wound, fibroblasts duplicate themselves rapidly. Oxygen could affect this replication. The effect of oxygen on collagen synthesis could be directly on the assembly of the molecule or, alternatively, on production of energy for the assembly. The evidence suggests that the hypoxia has its effects at all these points. The inclusion of each amino acid into the collagen of a proteoglycan molecule requires several molecules of ATP, and they are most efficiently derived from aerobic metabolism. Wound tissue reflects its precarious metabolic position by containing a rich supply of

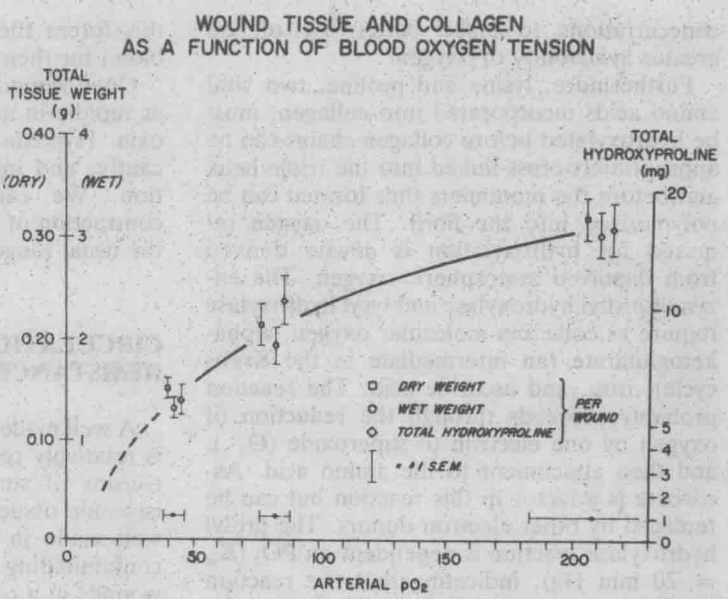

Figure 1–5. The relationship of arterial PO_2 to collagen (hydroxyproline) deposition in dead space wounds. The wounds were implanted wire mesh cylinders, and the values represent the tissue that grows into them by 20 days. The changes are far greater than those predicted by the change in oxygen *content* of blood and are, therefore, more proportional to PO_2 change. (From Hunt TK, Pai MP. Effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynec Obstet. 135:561, 1972. By permission of Surgery, Gynecology & Obstetrics.)

enzymes required for anaerobic energy metabolism. As wound oxygen tension falls, glucose consumption rises and energy production shifts even further to the glycolytic pathway with lactate as the "end product." This reaction occurs over almost the entire range of oxygen tension seen in human dead space wounds and indicates that energy production by fibroblasts is probably limited by any decrement in oxygen supply (Fig. 1–6). When more oxygen is presented to fibroblasts, they use it immediately and will subsequently readjust their enzyme

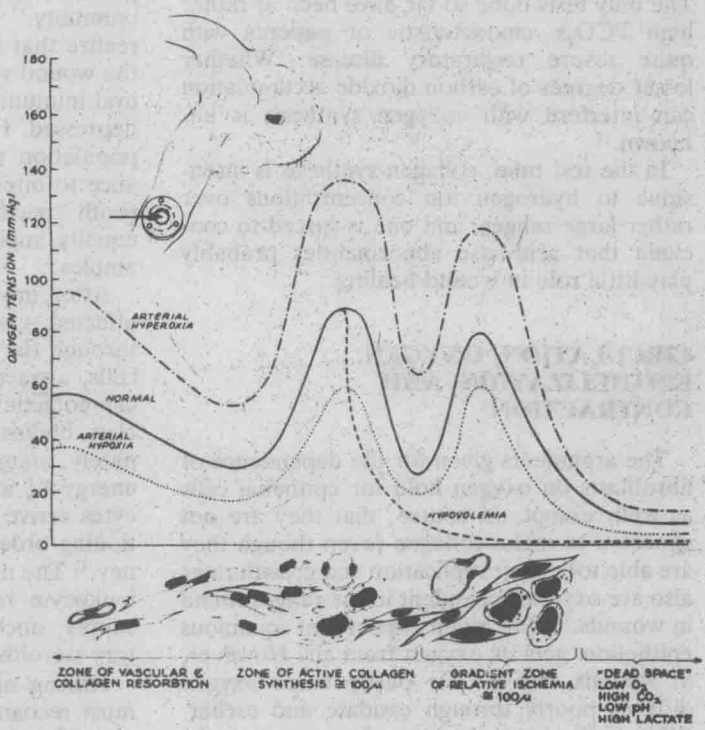

Figure 1–6. Schematic drawing of a cross-section of a rabbit ear chamber. This is a cross-section of Figures 1–1, 1–2, and 1–3. The measured PO_2 "profiles" are shown for hypoxia, normoxia, and hyperoxia. The effect of hypovolemia is shown as well; wound PO_2 is unaffected by hyperoxia during hypovolemia. Note that the slope of the gradient, i.e., the oxygen concentration, is proportional to arterial PO_2. (From Dunphy JE, Way L (eds.). Current Surgical Diagnosis and Treatment. 3rd ed. Los Altos, CA, Lange Medical Publications, 1977.)

concentrations to make better use of the greater availability of oxygen.

Furthermore, lysine and proline, two vital amino acids incorporated into collagen, must be hydroxylated before collagen chains can be appropriately cross-linked into the triple helix and before the monomers thus formed can be polymerized into the fibril. The oxygen required for hydroxylation is *always* derived from dissolved atmospheric oxygen. The enzymes prolyl hydroxylase and lysyl hydroxylase require as cofactors molecular oxygen, alpha-ketoglutarate (an intermediate in the Krebs cycle), iron, and ascorbic acid. The reaction probably proceeds through the reduction of oxygen by one electron to superoxide (O_2^-), and then attachment to the amino acid. Ascorbate is a factor in this reaction but can be replaced by other electron donors. The prolyl hydroxylase reaction is dependent on PO_2 (K_m = 20 mm Hg), indicating that the reaction loses velocity when PO_2 falls. Obviously, the PO_2 dependency is in the range of oxygen tensions seen in wounds and in the range in which the surgeon can influence them both with surgical technique and with supportive care of the patient's cardiopulmonary physiology.

For reasons unknown, increased carbon dioxide tensions depress collagen synthesis. The only tests done so far have been at rather high PCO_2s, characteristic of patients with quite severe respiratory disease. Whether lesser degrees of carbon dioxide accumulation can interfere with collagen synthesis is unknown.[31]

In the test tube, collagen synthesis is insensitive to hydrogen ion concentrations over rather large ranges, and one is forced to conclude that acid-base abnormalities probably play little role in wound healing.

CIRCULATION, OXYGEN, EPITHELIZATION, AND CONTRACTION

The arguments given for the dependence of fibroblasts on oxygen hold for epithelial cells as well, except, of course, that they are not expected to make collagen (even though they are able to). Their replication and growth rates also are oxygen dependent in the ranges found in wounds.[18] One might expect that squamous epithelium gets its oxygen from air. However, in wounds this is only partly true. Oxygen diffuses poorly through exudate and eschar. White cells also use oxygen. In many wounds, this forces the epithelial cells to depend on blood for their oxygen supply.[30]

Open wounds in normal animals heal almost as rapidly in normoxic conditions as in hyperoxia. Hypoxia, however, slows repair significantly, and influences the rate of epithelization. We cannot find any evidence that contraction of wounds is oxygen dependent in the usual range of PO_2.[25]

CIRCULATION, OXYGEN, AND RESISTANCE TO INFECTION

A well made and well tended surgical wound is relatively resistant to infection. One of the truisms of surgery is that wounds made in ischemic tissue will become infected. Wounds well made in healthy tissue can resist more contaminating organisms than roughly made wounds in a compromised tissue or host. This much is obvious. We have come to realize, however, that this observation, made by generations of surgeons, can be more accurately expressed: In effect, *anything* that interferes in *any* way with circulation or oxygen delivery to *any* degree will tend to increase susceptibility to infection.

Wounds possess an innate "immunity." This portion of host defense often is called "natural immunity." In recent years we have come to realize that it is the principal means by which the wound survives microbial challenges. Natural immunity can be temporarily elevated or depressed. For instance, changes in leukocyte population are critically important to resistance to infection. Changes in opsonic activity (both specific and nonspecific opsonins) are equally important. There are many other examples.

After injury, leukocytes marginate on the affected vascular endothelial cells and slip through the now leaky barrier between these cells, attracted by any of a large number of chemotactic substances, which range from foreign bodies to complement factors. Fortunately, margination and migration can use the energy of anaerobic metabolism, and leukocytes arrive at the target area in good functioning order despite the hazards of the journey.[12] The major hazards to this portion of the leukocyte response are poor regional blood supply, uncontrolled diabetes, anti-inflammatory steroids, and poor leukocyte mobility.

Having arrived in the wound, phagocytes must recognize their target. At this step, the natural and specific immune mechanisms over-