Using Physiology to Improve Surgical Wound Outcomes

Christiane Ueno, M.D.
Thomas K. Hunt, M.D.
Harriet W. Hopf, M.D.

San Francisco, Calif.

Summary: Despite major advances in surgical management and approaches, including aseptic techniques, prophylactic antibiotics, and laparoscopic surgery, surgical wound infection and wound failure remain common complications of surgery. In a review of the literature, the authors found that a growing body of literature supports the concept that patient factors are a major determinant of wound outcome after surgery. In particular, wounds are exquisitely sensitive to hypoxia, which is both common and preventable. Perioperative management can be adapted to promote postoperative wound healing and resistance to infection. The most important factors are fluid management, temperature management, pain control, increased arterial oxygen tension, and, as has been long recognized, appropriate sterile techniques and administration of prophylactic antibiotics. This article reviews how knowledge of and attention to physiology can improve quality of care in both acute and chronic wounds. (*Plast. Reconstr. Surg.* 117 (Suppl.): 59S, 2006.)

Despite major advances in surgical management, including aseptic techniques and prophylactic antibiotics, and advances in surgical approaches, such as laparoscopic surgery, surgical wound infection and wound failure remain common complications of surgery (Fig. 1). Wound complications are associated with prolonged hospitalization, increased resource consumption, and even increased mortality rates. More than 300,000 surgical infections occur each year in the United States at an estimated cost of more than $1 billion.[1] A growing body of literature supports the concept that patient factors are a major determinant of wound outcome after surgery. In particular, wounds are exquisitely sensitive to hypoxia, which is both common and preventable. Perioperative management can be adapted to promote postoperative wound healing and resistance to infection. The most important factors are fluid management, temperature management, pain control, increased arterial oxygen tension (PaO_2), and, as has been long recognized, appropriate sterile techniques and administration of prophylactic antibiotics. All but the last relate particularly to maintaining perfusion and oxygenation of the wound. This article reviews and discusses how knowledge of and attention to physiology can improve quality of care.

From the University of California, San Francisco, Wound Healing Laboratory, Departments of Anesthesia and Perioperative Care and Surgery.
Received for publication February 1, 2006; revised March 20, 2006.

DOI: 10.1097/01.prs.0000225438.86758.21

WOUND REPAIR

A surgical incision disrupts the skin barrier, creating an acute wound, and requires the ability to clean foreign material and resist infection. This response initiates a sequence of events, known as healing, that starts with any source of injury disturbing the equilibrium in the local environment, including the microcirculation.

Injury damages the local circulation and causes platelets to aggregate and release a variety of substances, including chemoattractants and growth factors. The initial result is coagulation, which prevents exsanguination but also widens the area that is no longer perfused. Bradykinin, complement, and histamine released by mast cells also perturb the microcirculation. Inflammatory cells (polymorphonuclear leukocytes immediately and macrophages by 24 to 48 hours) migrate to the wound and are activated in response to endothelial integrins, fibrin, lactate, hypoxia, foreign bodies, and growth factors. In turn, macrophages and lymphocytes produce more growth factors (including insulin-like growth factor-1, leukocyte growth factor, interleukins 1 and 2, transforming growth factor-β, and vascular endothelial growth factor[2]) and lactate.[2] This inflammatory

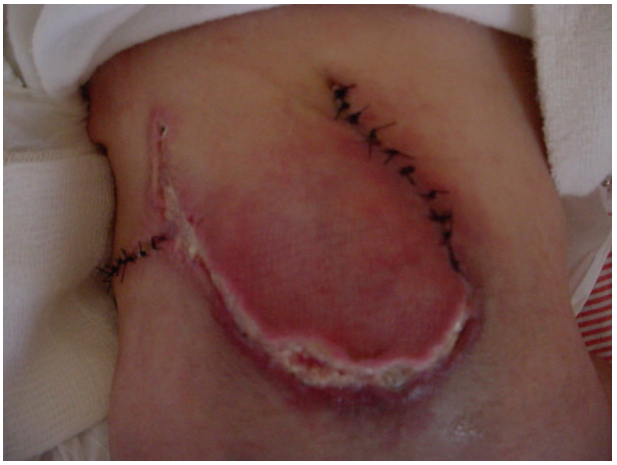

Fig. 1. Superficial dehiscence of incision with signs of inflammation on the back of a child with spina bifida who underwent repair with a Lynberg flap.

phase is characterized by erythema and edema of the wound edges.

Disruption of the normal skin barrier requires that wounds have the ability to clear foreign material and resist infection. Neutrophils provide nonspecific immunity and prevent infection. In the absence of infection, they disappear by about 48 hours. Nonspecific phagocytosis and intracellular killing are the major pathways activated in wounds.[3]

Nonspecific immunity by neutrophils depends on a high partial pressure of oxygen. This is because reactive oxygen species are the major component of the bactericidal defense against wound pathogens. After phagocytosis of the pathogen, nicotinamide adenine dinucleotide phosphate–linked oxygenase (also called phagosomal oxidase or primary oxidase), present in the phagocytic membrane, uses oxygen as the substrate to catalyze the formation of superoxide. Superoxide is bactericidal, but more importantly it initiates a series of cascades that produce other oxidants that increase bacterial killing capacity (Fig. 2). For example, in the presence of superoxide dismutase, superoxide is reduced to hydrogen peroxide. Hydrogen peroxide combines with chloride and, in the presence of myeloperoxidase, forms the bactericidal hypochlorous acid (the active ingredient in bleach).[4,5] Because intraphagosomal oxidant production depends on conversion of oxygen to superoxide, the process is exquisitely sensitive to the partial pressure (not content or saturation) of oxygen in the tissue. The half-maximal velocity for the phagosomal oxidase using oxygen as a substrate is 40 to 80 mmHg. This means that resistance to infection is critically impaired by wound hypoxia and becomes more efficient as partial pressure of oxygen increases even to very high levels (500 to 1000 mmHg).[6]

Oxidants produced by inflammatory cells have a dual role in wound repair. Not only are they central to resistance to infection but they also play a major role in initiating and directing the healing process. Oxidants, and in particular hydrogen peroxide produced via the respiratory burst, increase angiogenesis (via production of vascular endothelial growth factor) and collagen deposition in vitro and in vivo.[7]

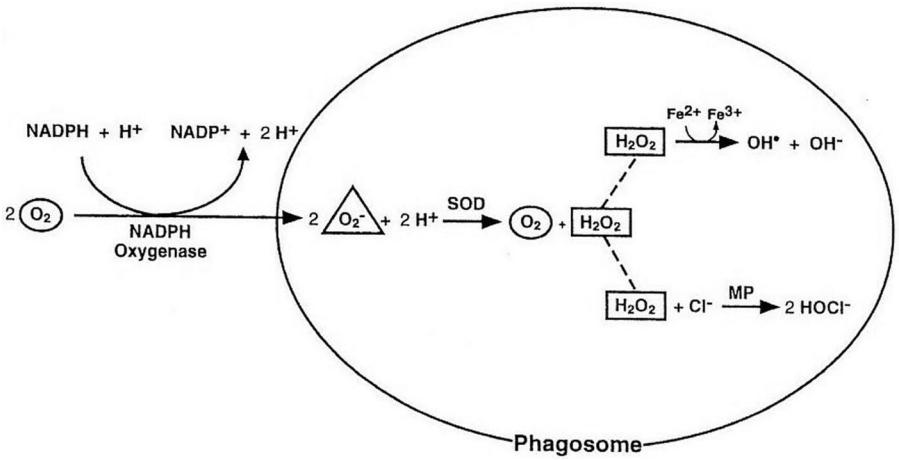

Fig. 2. Schematic of superoxide and other oxidant production within the phagosome (*NADPH*, nicotinamide adenine dinucleotide phosphate). Reprinted with permission from Hunt, T. K., and Hopf, H. W. Wound healing and wound infection: What surgeons and anesthesiologists can do. *Surg. Clin. North Am.* 77: 587, 1997.

Activated inflammatory cells consume oxygen at a high rate; coupled with the impaired microcirculation, this results in hypoxia, especially at the center of the wound.[8] Lactate is produced both anaerobically and aerobically, and this results in concentrations of 5 to 10 mM even in well-oxygenated wounds.[9] Lactate is a strong stimulus for collagen secretion and angiogenesis.[10,11] Anti-inflammatory steroids impair healing by suppressing inflammation at this step.

The proliferative phase begins approximately 4 days after injury, concurrent with a waning of the inflammatory phase. It consists of granulation tissue formation and epithelization. Granulation involves angiogenesis and synthesis of collagen and connective tissue proteins. Angiogenesis is required to replace the injured microcirculation and involves the movement of endothelial cells in response to three waves of growth factors. The first wave of growth factors comes with the release by platelets of platelet-derived growth factor, transforming growth factor-β, insulin-like growth factor, and others during the inflammatory phase. The second wave comes from fibroblast growth factor released from normal binding sites on connective tissue molecules. The third and dominant wave comes from vascular endothelial growth factor, delivered largely by macrophages stimulated by fibrinopeptides, hypoxia, and lactate.[12] Although it is usually present, hypoxia is not required for granulation, because of constitutive (aerobic) lactate production by inflammatory cells and fibroblasts. Too little lactate leads to inadequate granulation, while levels in excess of about 15 mM (usually associated with excess inflammation or infection) delay granulation.[13] The capillary endothelial response to angiogenic agents (i.e., migration into the wound, tubule formation, and connecting to sources of blood flow) requires oxygen, so that angiogenesis progresses proportional to blood perfusion and arterial partial pressure of oxygen.[14]

New blood vessels grow into the matrix that is produced by fibroblasts. Although fibroblasts replicate and migrate mainly in response to growth factors and chemoattractants, production of mature collagen requires oxygen.[15–17] Lactate, hypoxia, and some growth factors induce collagen mRNA synthesis and procollagen production. Posttranslational modification by prolyl and lysyl hydroxylases is required to allow collagen peptides to aggregate into triple helices. Collagen can only be exported from the cell when it is in this triple helical structure. The helical configuration is also primarily responsible for tissue strength. The activity of the hydroxylases is critically dependent on vitamin C and tissue oxygen tension.[17] Wound strength, which results from collagen deposition, is, therefore, highly vulnerable to wound hypoxia.

Angiogenesis and extracellular matrix (primarily collagen) production are closely linked. Fibroblasts cannot produce mature collagen in the absence of mature blood vessels that deliver oxygen to the site. On the other hand, new blood vessels cannot mature without a strong collagen matrix. Mice kept in a hypoxic environment (13% inspired oxygen) develop some new blood vessels in a test wound (with vascular endothelial growth factor or lactate added), but these vessels are immature, with little surrounding matrix, and demonstrate frequent areas of hemorrhage.[18]

Epithelization is characterized by replication and migration of epithelial cells across the skin edges. In acute wounds that are primarily closed, it is normally completed in 1 to 3 days. As with immunity and granulation, epithelization depends on growth factors and oxygen. Silver[19] and Medawar[20] demonstrated that the rate of epithelization depends on local oxygen in vivo. Topical oxygen (applied so that it does not dry out epithelial cells) has been advocated as a method to increase the rate of epithelization.[21] In contrast, O'Toole et al. demonstrated that hypoxia increases epithelial migration in vitro.[22] This may be explained, at least in part, by the dependence of epithelization on the presence of a bed of healthy granulation tissue, which is known to be oxygen dependent. Once epithelization is achieved, the skin barrier is restored and cover dressings become optional. In open wounds, epithelization occurs only after the wound space is filled with granulation tissue.

The final phase of wound repair is maturation, which involves ongoing remodeling of the granulation tissue and increasing wound tensile strength. The movement of fibroblasts pulls the collagen fibers together, promoting contraction of the tissue. This contraction is responsible for shortening scars and shrinking wounds, and it is inhibited by the use of steroids in doses greater than 30 mg/day.[23]

WOUND PERFUSION AND OXYGENATION

Complications of wounds include failure to heal, infection, and excessive scarring or contracture. Rapid repair has the least potential for infection and excess scarring. The surgeon's goals, therefore, are to avoid contamination, ensure rapid tissue synthesis, and optimize the immune

response. All surgical procedures lead to some degree of contamination that must be controlled by local host defenses. The initial hours after contamination represent a decisive period during which inadequate local defenses may allow an infection to become established.

Normally, wounds on the extremities and trunk heal more slowly than those on the face. The major difference in these wounds is the degree of tissue perfusion and thus the wound tissue oxygen tension. As a rule, repair proceeds most rapidly and immunity is strongest when wound oxygen levels are high, and this is only achieved by maintaining perfusion of injured tissue.[24] Ischemic or hypoxic tissue, on the other hand, is easily infectable and heals poorly if at all. Wound tissue oxygenation is complex and depends on the interaction of blood perfusion, arterial oxygen tension, hemoglobin dissociation conditions, carrying capacity, mass transfer resistances, and local oxygen consumption. Wound oxygen delivery depends on vascular anatomy, the degree of vasoconstriction, and arterial partial pressure of oxygen (Fig. 3).

The standard teaching that oxygen delivery depends more on hemoglobin-bound oxygen (oxygen content) than on arterial partial pressure of oxygen may be true of working muscle, but it is not true of wound healing. In muscle, intercapillary distances are small and oxygen consumption is high. In subcutaneous tissue, on the other hand, intercapillary distances are large and oxygen consumption is relatively low.[25] In wounds, in which the microvasculature is damaged, diffusion distances increase by an order of magnitude. Peripheral vasoconstriction further increases diffusion distance.[8] The driving force of diffusion is partial pressure. Hence, a high partial pressure of oxygen is needed to force oxygen into injured and healing tissues, particularly in subcutaneous tissue, fascia, tendon, and bone, the tissues most at risk for poor healing.

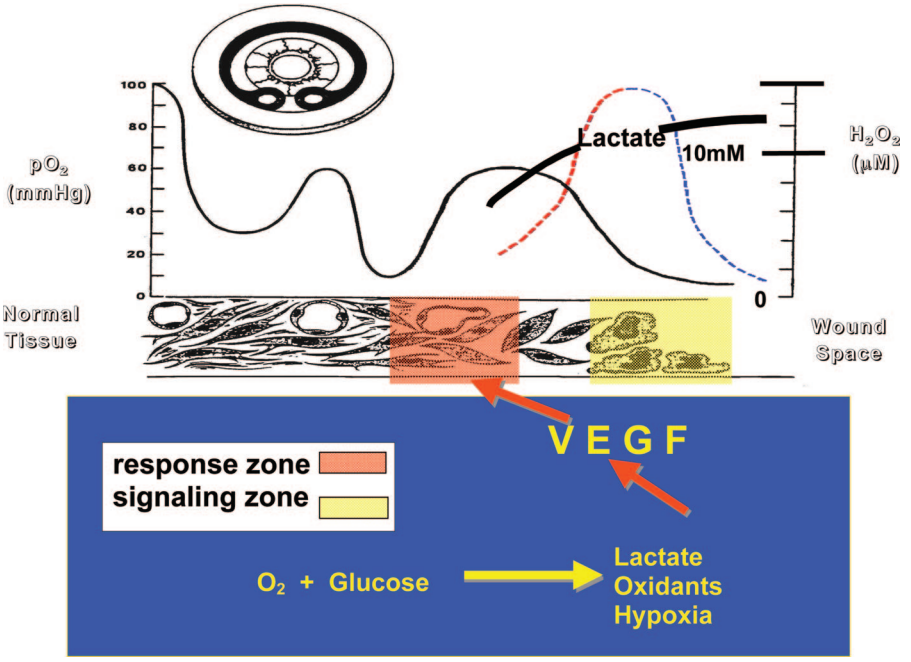

Fig. 3. The wound module. Cross-section of the wound module in a rabbit ear chamber (*above, left*, diagram of chamber). Note that partial pressure of oxygen (pO_2), depicted graphically above the cross-section, is highest next to the vessels, with a gradient down to zero at the wound edge. Note also the lactate gradient, which is high in the dead space and lower (but still above plasma) toward the vasculature. Hydrogen peroxide is present at fairy high concentrations and is also a major stimulus to wound repair (from Sen, C. K., Khanna, S., Babior, B. M., Hunt, T. K., Ellison, E. C., and Roy, S. Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. *J. Biol. Chem.* 277: 33284, 2002). Modified figure reprinted with permission from Silver, I. A. The physiology of wound healing. In T. K. Hunt and J. E. Dunphy (Eds.), *Fundamentals of Wound Management.* New York: Appleton-Century-Crofts, 1980. P. 30.

Although oxygen consumption is relatively low in wounds, it is consumed by processes that require oxygen at a high concentration. Inflammatory cells use little oxygen for respiration, producing energy largely via the hexose-monophosphate shunt.[6] Most of the oxygen consumed in wounds is used for oxidant production (bacterial killing), with a significant contribution as well for collagen synthesis, angiogenesis, and epithelization. The rate constants (half-maximal velocity) for oxygen for these components of repair all fall within the physiologic range of 25 to 100 mmHg.[5,6,15,16,20,26]

Because of the high rate constants for oxygen substrate for the components of repair, the rate at which repair proceeds varies according to tissue partial pressure of oxygen from zero to at least 250 mmHg. In vitro fibroblast replication is optimal at a partial pressure of oxygen of about 40 to 60 mmHg. Neutrophils lose their ability to kill bacteria in vitro below about 40 mmHg.[27,28] These in vitro observations are clinically relevant. "Normal" subcutaneous partial pressure of oxygen, measured in test wounds in uninjured, euthermic, euvolemic volunteers breathing room air, is 65 ± 7 mmHg.[29] Thus, any reduction in wound partial pressure of oxygen may impair immunity and repair. In surgical patients, the rate of wound infections is inversely proportional,[30] while collagen deposition is directly proportional,[31] to postoperative subcutaneous wound tissue oxygen tension.

High oxygen tensions (>100 mmHg) can be reached in wounds, but only if perfusion is rapid and arterial partial pressure of oxygen is high.[27,32] This is because (1) subcutaneous tissue serves a reservoir function, so there is normally flow in excess of nutritional needs, and (2) wound cells consume relatively little oxygen, about 0.7 ml/100 ml of blood flow at a normal perfusion rate.[25,33] At high levels of arterial oxygen tension, this small volume can be carried by plasma alone. Contrary to popular belief, therefore, oxygen-carrying capacity (i.e., hemoglobin concentration) is not particularly important to wound healing, provided that perfusion is normal.[34] Wound partial pressure of oxygen and collagen synthesis remain normal in individuals who have hematocrit levels as low as 15 to 18 percent, provided they can appropriately increase cardiac output and vasoconstriction is prevented.[35,36]

Peripheral vasoconstriction, which results from central sympathetic control of subcutaneous vascular tone, is probably the most frequent and clinically the most important impediment to wound oxygenation. Subcutaneous tissue is both a reservoir to maintain central volume and a major site of thermoregulation. There is little local regulation of blood flow, except by local heating.[37,38] Therefore, subcutaneous tissue is particularly vulnerable to vasoconstriction. Sympathetically induced peripheral vasoconstriction is stimulated by cold, pain, fear, and blood volume deficit[39,40] and by various medications, including smoking (nicotine),[29] beta-adrenergic antagonists, and alpha-1 agonists, all commonly present in the perioperative environment. Perioperative hypothermia is common and results from anesthetic drugs, exposure to cold, and redistribution of body heat. Blood loss and increases in insensible losses (third spacing) increase fluid requirements in the perioperative period, thereby leaving the patient vulnerable to inadequate fluid replacement. Thus, vasomotor tone is, to a large degree, under the surgeon's control.[39,40]

Prevention or correction of hypothermia[41] and blood volume deficits[42] has been shown to decrease wound infections and increase collagen deposition in patients undergoing major abdominal surgery. Preoperative systemic (forced air warmer) or local (warming bandage) warming have also been shown to decrease wound infections, even in clean, low-risk operations such as breast surgery and inguinal hernia repair.[43] Subcutaneous tissue oxygen tension is significantly higher in patients with good pain control than it is in those with poor pain control after arthroscopic knee surgery.[44] Stress also causes wound hypoxia and significantly impairs wound healing and resistance to infection.[45,46] These effects are clearly mediated, in large part, by raising the partial pressure of oxygen in the injured tissue.

Greif et al. demonstrated in a randomized, controlled, double-blind trial that, in warm, well-hydrated patients with good pain control, that is, in well-perfused patients (n = 500) undergoing major colon surgery, administration of 80% versus 30% oxygen intraoperatively and for the first 2 postoperative hours significantly reduced the wound infection rate by 50 percent.[47] Belda et al.[48] recently replicated these results (significant 40 percent reduction in surgical site infection) in a randomized, controlled, double-blind trial in 300 colon surgery patients randomized to 80% versus 30% oxygen intraoperatively and during the first 6 postoperative hours. Surgical and anesthetic management were standardized and intended to support optimal perfusion. A smaller (n = 165) randomized, controlled study by Pryor et al.[49] demonstrated a doubling of surgical site infection in patients randomized to 80% versus 35% oxygen

intraoperatively. There were a number of methodological flaws in the study, but, more importantly, the two groups of patients were not equivalent, which likely explained the increase in infections seen in the 80% oxygen group. Thus, there is substantial evidence that using 80% inspired oxygen intraoperatively and providing supplemental oxygen postoperatively in *well-perfused* patients will reduce the risk of wound infection.

Delivery of antibiotics also depends on perfusion. Parenteral antibiotics given so that high levels are present in the blood at the time of wounding clearly diminish, but do not eliminate, wound infections.[50] In about one third of all wound infections, the bacteria cultured from the wound are sensitive to the prophylactic antibiotic given to the patient, even when the antibiotics are given according to standard procedure.[50] The vulnerable third of patients appear to be the hypoxic and vasoconstricted group. When antibiotics are present in the wound at the time of injury, they are trapped in the fibrin clot at the wound site, where they may have efficacy against contaminating organisms. Antibiotics diffuse poorly into the fibrin clot, however, so that later administration, whether more than 2 hours after injury or in response to wound infection, will have little effect. On the other hand, oxygen diffuses easily through the fibrin clots and is effective even 6 hours after contamination.[51]

Some chronic diseases, particularly those that affect the microcirculation, such as diabetes and hypertension, increase the rate of wound dehiscence.[52] In diabetic patients, for example, tight glucose control is crucial. Blood glucose should be monitored closely and maintained in the normoglycemic range.[23] The chronic disease score, a measurement of health status as a function of age, sex, and 29 chronic diseases, predicted surgical site infection more accurately than a Centers for Disease Control predictor, the National Nosocomial Infections Surveillance System score, which includes duration of the surgery, class of the wound, and the American Society of Anesthesiologists score.[53]

NUTRITION

Skin is the largest and most readily examined organ in the body. It is therefore not surprising that many nutritional deficiencies present with alterations in the skin or in healing. This led to the recognition of the importance of nutrition in wound healing. Nutritional requirements change during the healing process. The initial response to injury is catabolic energy production. This must convert to an anabolic response with protein synthesis in order for healing to occur. In general, specific nutritional requirements are not well delineated. Recent intake is most important.[54,55]

Proteins are essential for the anabolic phase and are degraded in catabolic states such as sepsis, burns, and major orthopedic injury (femur fracture). Thus, calculation of the nitrogen balance gives an idea of the amount of protein lost and the required level for replacement. The major protein of the skin is collagen. Use of specific amino acids has no clear benefit. Arginine, a precursor of proline, and glutamine, a precursor of nucleotide synthesis, both accelerate wound repair when given in doses of 15 to 30 g/day. This appears to be more a pharmacologic than nutritional effect.[56,57]

Scurvy, the nutritional defect induced by vitamin C deficiency, has been recognized since the fifteenth century, when poor healing and hematoma formation were described in sailors by the Portuguese explorer Vasco da Gama. The British Naval physician James Lind performed the first known randomized, controlled trial in 1747 and demonstrated the efficacy of citrus fruits in preventing scurvy (the etiology remained unknown until the description of vitamin C in the twentieth century). Vitamin C levels decrease rapidly in injured and infected or septic patients; thus, supplemental vitamin C (500 mg twice daily) should be given to all patients with wounds or traumatic injuries. Vitamin C is a cofactor for prolyl hydroxylase, the same reaction for which oxygen is a rate-limiting substrate. Wound hypoxia thus, to a degree, mimics scurvy.

Vitamin A[58] is a proinflammatory vitamin that is associated with differentiation and growth of the epidermis. Deficiency, although uncommon, is associated with impaired healing. Vitamin A (25,000 IU daily) also been demonstrated to reverse the impaired healing associated with steroid use,[59] diabetes,[60] and radiation.[61] Because it is a fat-soluble vitamin and excess intake is associated with adverse effects, it should be given for only 10 days. Topical vitamin A (available over the counter), applied daily directly to the open wound, is a useful alternative.

Among trace elements, zinc is the oldest known medicinal treatment, and was described by the ancient Egyptians for skin wounds.[57] Zinc is involved in DNA and RNA synthesis. Zinc deficiency impairs healing. There is no evidence, however, that zinc supplementation accelerates healing in patients without a deficiency. However, a short course (220 mg orally, daily for 10 days) is

recommended in wound patients to address any unrecognized deficiencies.

Carbohydrates are also necessary for collagen synthesis. It is estimated that a wound 3 cm^2 in surface area and 1 mm in depth contains 10 mg of collagen, requiring 9 kcal of energy to produce (900 cal/1 g of collagen).[57,62] Omega-3 fatty acids may modulate the arachidonic acid pathway (inflammatory pathway) and thereby influence wound maturation.[57]

PREOPERATIVE PREPARATION

Given our knowledge of the physiology of wound healing, what are the best strategies to ensure optimal healing? Wound infection, flap failure, and dehiscence are dreaded complications of plastic surgery. To the degree they are predictable, interventions can be targeted at those patients most at risk (Table 1).

The Centers for Disease Control, in the Study of the Effect of Nosocomial Infection Control," or SENIC,[63] developed a remarkably useful and simple predictive tool based on a score of 0 or 1 for each of the following four patient factors: an abdominal operation, an operation that lasts 2 hours or more, a surgical site that is contaminated or infected, and a patient who will have three or more diagnoses at discharge, exclusive of wound infection. The risk of infection with a score of 0 is 1 percent, that with a score of 1 is 3.6 percent, with a score of 2, 9 percent, with a score of 3, 17 percent, and with a score of 4, 27 percent. These percentages may seem high, but this index was constructed on 3 percent of the American surgical patients in 1975 to 76 and 1983, and the overall results are consistent with numerous other studies. More recent risk analyses by the same group, based on simpler predictors (e.g., American Society of Anesthesiologists Physical Status Classification) have yielded less sensitivity but about the same overall infection rate.[64]

Modifiable risks include smoking, malnutrition, hypercholesterolemia, and hypertension. These should be assessed and corrected when possible before surgery. The decision to delay surgery must take into account both the urgency of the surgery and the severity of the risk.

Table 1. Preoperative Checklist

- Assess and optimize cardiopulmonary function; correct hypertension
- Treat vasoconstriction: attend to blood volume, thermoregulatory vasoconstriction, pain, and anxiety
- Assess recent nutrition and treat as appropriate
- Treat existing infection; among other actions, clean and treat skin infections
- Assess wound risk by SENIC score, in order to decide upon the extent to which prophylactic measures should be taken
- Start vitamin A or anabolic steroids in patients taking prednisone
- Improve or maintain blood sugar control

SENIC, Study of the Effect of Nosocomial Infection Control.
Used with permission from Hunt, T. K., and Hopf, H. W. Wound healing and wound infection: What surgeons and anesthesiologists can do. *Surg. Clin. North Am.* 77: 587, 1997.

ANTIBIOTIC PROPHYLAXIS

In 1958, Miles et al. [65] used a guinea pig model for the proof of principle that administration of an antibiotic before contamination (incision) could reduce the risk of surgical site infection. The first controlled clinical trial in antibiotic prophylaxis was performed in 1960 by two surgeons at Washington University, St. Louis, Harvey Bernard and Bill Cole. They showed the efficacy of antibiotic prophylaxis. The incorporation of antibiotic practice was slow, and only after a number of further studies was it adopted as standard care for at-risk procedures.[66]

Centers for Disease Control guidelines generally do not specify antibiotic agents, although they give rationales for various choices.[67] The agent for antibiotic prophylaxis must cover the most likely spectrum of bacteria present in the surgical field. The most commonly used antibiotic for prophylaxis is cefazolin, a first-generation cephalosporin, because the potential pathogens for the vast majority of operations come from the skin (Gram-positive cocci).[66,67]

By definition, prophylactic antibiotics are given preoperatively or intraoperatively. The exact timing for the administration of the antibiotic depends on the pharmacology and half-life of the drug. Timing is crucial for antibiotic prophylaxis. The benefits of prophylaxis decrease if the antibiotic is given more than 2 hours before or after incision. Ideally, the prophylaxis should be administered within 30 minutes to 1 hour of incision.[50,65,66,68] An adequate, weight-based dose should be given. Depending on their half-lives, administration of antibiotics should be repeated during long operations or in patients with large blood loss.[69] For cefazolin, for example, which is normally given every 8 hours, the dose should be repeated every 4 hours intraoperatively.[69] Finally, prophylactic antibiotics should be discontinued at the end of the operation, or at least by 24 hours. Prolonging the course of prophylactic antibiotics does not reduce the risk of infection but does increase the risk of adverse consequences of antibiotic administration.[67]

Unfortunately, methicillin-resistant *Staphylococcus aureus* is becoming more common. Although it varies by country, region, and hospital, about 60 percent of *S. aureus* are methicillin-resistant. Among the independent risk factors identified for methicillin-resistant *S. aureus* infection are prolonged use of prophylaxis, use of drains for more than 24 hours, and the number of procedures performed on the patient. Hand hygiene (alcohol gel kills more than 99.9 percent of transient pathogens, including methicillin-resistant *S. aureus*) is among the most effective means of preventing the development of methicillin-resistant *S. aureus*, as well as cross-contamination of patients with any organism.

INTRAOPERATIVE MANAGEMENT

Careful surgical technique is fundamental to optimal wound healing (Table 2). Delicate handling of the tissue, adequate hemostasis, and surgeon experience lead to healthier wounds. Plan incisions with regard to blood supply, particularly when operating near or in old incisions. Release mechanical retractors from time to time to allow perfusion to the wound edges. Judicious antibiotic irrigation of contaminated areas may be effective. Since dried wounds lose perfusion, keep wounds moist, especially during long operations. Not all wounds can be anatomically closed. Edema, obesity, the possibility of unacceptable respiratory compromise, and need to débride abdominal or chest wall tissues can all interfere with wound closure. A variety of polymeric "fabrics" is available to interpose between the wound edges when this occurs. Their use is preferable to evisceration on the one hand or respiratory compromise on the other. If the problem is temporary, the implant can be removed in a few days. A variety of prostheses, both synthetic and biodegradable, are available to interpose between the wound edges. Polypropylene mesh prosthesis is the most common used. Polypropylene mesh permits the growth of granulation tissue above it, and it can be used in the presence of infection. On the other hand, it has been associated with bowel adhesion and posterior bowel fistulas or perforation. Mathes et al.[70] reported complications in less than 8 percent of cases using this mesh prosthesis for abdominal wall reconstruction. Absorbable prostheses such as AlloDerm are also available. AlloDerm is made of acellular cadaver dermis. It is thought that AlloDerm permits an influx of new vessels and posterior reabsorption while preventing complications such as bowel adhesion and perforation or extrusion. However, there are still no data on long-term follow-up. The choice of prosthesis depends mainly on the surgeon's experience.

Table 2. Intraoperative Management

- Appropriate prophylactic antibiotics should be given at the start of any procedure in which infection is highly probable and/or has potentially disastrous consequences; keep antibiotic levels high during long operations
- Keep patients warm
- Observe gentle surgical technique with minimal use of ties and cautery
- Keep wounds moist
- Use antibiotic irrigation in contaminated cases
- Elevate PaO2
- Delay closure for heavily contaminated wounds
- Use appropriate sutures (and skin tapes)
- Use appropriate dressings

Used with permission from Hunt, T. K., and Hopf, H. W. Wound healing and wound infection: What surgeons and anesthesiologists can do. *Surg. Clin. North Am.* 77: 587, 1997.

As the operation proceeds, new wounds are made and contamination continues. Thus, it is important not only to maintain the rhythm of the surgery but also to be aware of the management of the whole patient. All anesthetic agents tend to cause hypothermia (1) by causing vasodilation, which redistributes heat from core to periphery in previously vasoconstricted patients and increases heat loss, and (2) by decreasing heat production.[71] Vasoconstriction is uncommon intraoperatively, as the threshold for thermoregulatory vasoconstriction is decreased, but it is often severe in the immediate postoperative period, when anesthesia is discontinued and the thermoregulatory threshold returns to normal in the face core hypothermia. The onset of pain with emergence from anesthesia adds to this vasoconstriction.[44] Rapid rewarming using a forced air warmer for hypothermic patients in the postanesthesia care unit does appear to be effective,[72] although clearly prevention of hypothermia is the goal.[41] Maintenance of a high room temperature or use of forced air warming before, during, and after the operation is significantly more effective than other methods of warming, such as circulating water blankets placed under the patient and humidification of the breathing circuit.[73]

Replace fluid losses aggressively: 10 to 15 ml/kg per hour plus three to four times the blood loss (crystalloid) during major abdominal surgery. This takes into account third space losses as well as the preoperative fluid deficit, which is especially great after a bowel preparation. Dark venous blood in the incision usually indicates vasoconstriction, not arterial hypoxia. A recent study demonstrated significantly greater subcutaneous oxy-

gen tension, intraoperatively and in the postanesthesia care unit, in major abdominal surgery patients who received fluids at a rate of 16 to 18 ml/kg per hour versus 8 ml/kg per hour intraoperatively.[74] Warm patients are unlikely to develop pulmonary edema with a high rate of fluid administration, as they have excess capacitance due to vasodilation. Cold patients, on the other hand, are highly susceptible to pulmonary edema even after relatively small fluid boluses. Thermoregulatory vasoconstriction increases afterload, causing increased cardiac work. Moreover, administered fluid cannot open up constricted vessels until the hypothermic stimulus is removed; thus, there is virtually no excess capacitance in the system.

Address pain control intraoperatively, so that patients do not have severe pain upon emergence. Achieving the goal is more important than the technique used to do so. Although regional anesthesia/analgesia may provide superior pain relief, the effects of specific analgesic regimens on wound outcome have not yet been adequately studied.

For skin closure, monofilament sutures are preferable, and ideally they should be of the finest gauge compatible with the strength needed. The tendency to develop a suture sinus or stitch abscess depends on the size and material of the suture. In general, thinner suture materials (thinner than 4.0) exert a protective effect in the wound site.[75] The spectrum of time for absorption of the suture material is available and is based on the time of half-loss of suture strength. Polylactide sutures are most suitable for subcutaneous suturing and should be used deeply in the dermis to avoid extrusion of the suture material. Deep tissues, such as abdominal and chest walls, deep fascia, and synovium, can be closed with interrupted or running sutures, depending on strength of the tissue edges. Furthermore, sutures should not be too tight, to allow for the expected swelling of the tissues without causing ischemia. Irrigate out small particles, as fat debris, to remove devitalized tissue.

The dressing technique is not critical in primarily closed operative wounds, because resistance to external contamination builds rapidly, within a few hours. Pressure dressings should not be used routinely, as they reduce wound oxygen levels.[76] They may be appropriate in the setting of significant edema or risk of hematoma formation. Delayed primary closure should be considered when wound infection seems highly probable. Wisely used, delayed closure can prevent infection and unnecessary scarring. Closure can almost always be accomplished on the ward or in the office using skin tapes and no anesthesia.[77]

POSTOPERATIVE MANAGEMENT

Wounds are most vulnerable in the early hours after surgery (Table 3). Although antibiotics lose their effectiveness after the first hours, natural wound immunity (oxygen-related) lasts longer.[51] Even a short period of vasoconstriction during the first day is sufficient to reduce oxygen supply. Correction and prevention of vasoconstriction in the first 24 to 48 hours after surgery will have significant beneficial effects.[30] Strict glycemic control is also important.[30]

All vasoconstrictive stimuli must be corrected simultaneously to allow optimal healing. Volume is the last to be corrected, because vasoconstriction for other reasons induces diuresis and renders the patient hypovolemic (peripherally, not centrally). In patients undergoing major surgery, a 1-liter fluid bolus given 1 to 2 hours after the end of surgery should therefore be routine. These measures are particularly important in any patients at high risk for wound complications for other reasons (malnutrition, steroid use, diabetes, and so on) or when vasoconstrictive drugs, such as beta-blockers and alpha-agonists, are required for other reasons.

Local perfusion is not assured until patients have a normal blood volume, are warm and pain free, and are receiving no vasoconstrictive drugs, that is, until the sympathetic nervous system is inactivated. Warming should continue until patients are thoroughly awake and active and can maintain their own thermal balance. After major operations, warming may be useful for many hours or even days. The goal is skin warmth, and wound

Table 3. Postoperative Management

- Keep patients warm
- Provide analgesia to keep patients comfortable, if not pain free; patient report and the ability to move freely are the best signs of adequate pain relief
- Give only one more dose of antibiotic, unless an infection is present or contamination continues
- Keep up with third space losses; remember that fever increases fluid losses
- Assess perfusion and react to abnormalities
- Avoid diuresis until pain is gone and the patient is warm
- Assess losses (including thermal losses) if the wound is open
- Assess the need for parenteral/enteral nutrition and respond
- Continue to control hypertension and hyperglycemia

Used with permission from Hunt, T. K., and Hopf, H. W. Wound healing and wound infection: What surgeons and anesthesiologists can do. *Surg. Clin. North Am.* 77: 587, 1997.

vasoconstriction due to cold surroundings often coexists with core hyperthermia. Moderate hyperthermia is not, in itself, a problem. When extensive wounds are left open, warmth should be continued, and heat losses due to evaporation should be prevented to avoid vasoconstriction and to minimize caloric losses.

Assessing perfusion, especially in the postanesthesia care unit, is critical. Unfortunately, urine output is a poor, often misleading guide to peripheral perfusion.[78] Markedly low output may indicate decreased renal perfusion, but normal or even high urine output has little correlation to wound/tissue partial pressure of oxygen. Many factors commonly present in the perioperative period, including hyperglycemia, dye administration, thermoregulatory vasoconstriction, adrenal insufficiency, and various drugs, may cause inappropriate diuresis in the face of mild hypovolemia.

Physical examination of the patient is a better guide to dehydration and vasoconstriction. Assess vasoconstriction by a capillary return time of more than 2 to 3 seconds at the forehead and more than 5 seconds over the patella. Eye turgor is another good measure of hydration. Finally, patients can usually distinguish thirst from a dry mouth. Skin should be warm and dry.

Third space losses continue for about 24 hours and then abate. Using tissue oxygen probes, we find that the routine postoperative fluid order of 100 to 150 ml/hour is inadequate to maintain wound perfusion for the first 12 to 24 hours after most abdominal and chest operations.[78] Routine measurement of wound partial pressure of oxygen is not yet available, so it is useful to make assessment of the degree of vasoconstriction, an indirect indicator of wound partial pressure of oxygen, routine. In general, for large abdominal cases, 2 to 3 ml/kg per hour of intravenous fluids is sufficient for the first 12 to 24 postoperative hours. After that period, the intravenous rate should be significantly decreased, because of the decrease in third space losses and the start of mobilization of edema and other third space fluids.

When excessive tissue fluids have accumulated, diuresis should be undertaken gently so that transcapillary refill can maintain blood volume. This applies to patients who need renal dialysis as well. The average dialysis patient vasoconstricts sufficiently to lower tissue partial pressure of oxygen by 30 percent or more during dialysis and needs about 24 hours to return vasomotor tone and wound/tissue partial pressure of oxygen to normal.[79] Fluid losses from the vascular system are not necessarily replaced from the tissues as rapidly as they are sustained. Tissue edema may be the price paid for adequate intravascular volume. Edema increases intracapillary distance, so that there may be a delicate balance between excessive edema and peripheral vasoconstriction (which worsens the hypoxia caused by edema).

Vasoconstrictive drugs should be avoided. The most common and most avoidable is smoking. Beta blockers should be used only when they are clearly medically indicated.[80] Both are known to reduce wound/tissue partial pressure of oxygen. Clonidine is an alternative drug for heart rate control[81–83] that also induces vasodilation and may increase wound partial pressure of oxygen.[84] High-dose alpha-adrenergic agonists may cause harm by decreasing tissue partial pressure of oxygen, but in a limited experience, we have found that small doses, including so-called renal dose (3 to 5 μg/kg per minute) dopamine, have little or no effect on wound/tissue partial pressure of oxygen. It is important to remember that decreasing cardiac output may also reduce wound perfusion. Thus, a balance must be maintained between minimizing use of vasopressors and maintaining an adequate cardiac output.

Maintenance of tissue partial pressure of oxygen requires attention to pulmonary function postoperatively. Pain control appears important because it favorably influences both pulmonary function and vascular tone. This is particularly true in patients at high risk for pulmonary complications postoperatively, such as morbidly obese patients and those with pulmonary disease.[85] Epidural analgesia may be the route of choice in these patients. It has several advantages over parenterally administered opioids, in that it generally achieves lower pain scores with less sedation. Nonetheless, opioid-induced pruritus is more common with epidural administration and, in some patients, may be severe enough to counteract the benefits of pain control.

Patient controlled analgesia is also quite effective at achieving low pain scores. It also has the benefit of giving control to the patient, which leads to patient satisfaction as high as with epidural analgesia in many cases.[86] Nurse-administered, as-needed doses of intravenous or intramuscular opioids should be avoided, as inadequate pain control is common (often exceeding 50 percent) using this approach.[87] The key to pain control is recognition of the need for analgesia and attention to the patient's complaints of pain. Opioid requirements vary enormously and are not always predictable, but even tolerant patients (intravenous drug abusers or those with cancer pain)

can be given adequate pain relief with sufficient attention.

LONG-TERM FOLLOW-UP

Some wounds heal to excess. Hypertrophic scar and keloid are common forms of abnormal scar due to abnormal responses to healing. The distinction between them may be difficult. Hypertrophic scars are common after burns and correlate with the length of time required to close the wound. Rapid healing is less likely to become excessive. This is one of the strong arguments for early closure and the use of skin substitutes. Hypertrophic scars also tend to occur in wounds that cross lines of force in the skin. Hypertrophic scars occur within months or even right after the injury, do not grow beyond the wound edges, and often flatten spontaneously after 1 to 2 years. Hypertrophic scars that do not resolve spontaneously or interfere with function are often best treated surgically with revisions designed to relieve tension. They may also respond to pressure garments, repeated injections of steroids, or to prolonged dressing with thick silicone sheets.

Keloids occur within 1 year after injury and are more common in blacks, Hispanics, and Asians, with an incidence of 4.5 to 16 percent. Keloids usually are more painful than hypertrophic scars, pruritic, and grow beyond the edges of the wound without regression. They often occur on the shoulder, upper arm, anterior chest (particularly the presternal area), and upper back, but generally not on hands or below the groin. Keloid recurrence after incision is common, occurring about 50 to 80 percent of the time.[88] The pathophysiology and treatment of keloids and hypertrophic scars are covered in depth elsewhere in this issue.

Contractures occur when shrinking scars constrict mobility. All scars shrink, unless the force of contraction is balanced by stretching forces. In general, prophylactic efforts, braces, physical therapy, stretching, and pressure dressings are the most effective prevention and therapy. Special compression garments can be made. Established contractures that resist or recur are often best treated surgically by flaps, or so-called Z- or Y-plasty, which relax contractures and interpose normal tissues along the line of contracture.

Suture sinuses commonly occur after use of nonabsorbable or slowly absorbable suture near the skin. Their frequency is in proportion to the size of suture material used and the presence of prior wound infection. The cure is surgical removal of the offending stitch(es).

SUMMARY

In patients with moderate to high risk of surgical site infection, surgeons have the opportunity to enhance wound healing and prevent wound infections by simple, inexpensive, and readily available means.[89] Intraoperatively, appropriate antibiotic use, prevention of vasoconstriction (volume, warming), and maintenance of a high PaO2 (300 to 500 mmHg) are key. Postoperatively, the focus should remain on prevention of vasoconstriction through pain relief, warming, and adequate volume administration in the postanesthesia care unit.

Harriet W. Hopf, M.D.
Department of Anesthesia and Perioperative Care
University of California, San Francisco
Box 0648, Room U286
521 Parnassus Avenue
San Francisco, Calif. 94143-0648
harriet.hopf@hsc.utah.edu

ACKNOWLEDGMENT

This study was supported by National Institutes of Health grant NIGMS P50 27345.

REFERENCES

1. Kaye, K. S., Sands, K., Donahue, J. G., et al. Preoperative drug dispensing as a predictor of surgical site infection. *Emerging Inf. Dis.* 7: 57,2001.
2. Dvonch, V. M., Murphey, R. J., Matsuoka, J., and Grotendorst, G. R. Changes in growth factor levels in human wound fluid. *Surgery* 112: 18, 1992.
3. Babior, B. M. Oxygen-dependent microbial killing by phagocytes. *N. Engl. J. Med.* 198: 659, 1978.
4. Gabig, T. G., Bearman, S. I., and Babior, B. M. Effects of oxygen tension and pH on the respiratory burst of human neutrophils. *Blood* 53: 1133, 1979.
5. Edwards, S., Hallett, M., and Campbell, A. Oxygen-radical production during inflammation may be limited by oxygen concentration. *Biochem. J.* 217: 851, 1984.
6. Allen, D. B., Maguire, J. J., Mahdavian, M., et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch. Surg.* 132: 991, 1997.
7. Sen, C. K., Khanna, S., Babior, B. M., Hunt, T. K., Ellison, E. C., and Roy, S. Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. *J. Biol. Chem.* 277: 33284, 2002.
8. Silver, I. A. Cellular microenvironment in healing and nonhealing wounds. In T. K. Hunt, R. B. Heppenstall, and E. Pines (Eds.), *Soft and Hard Tissue Repair.* New York: Praeger, 1984. Pp. 50–66.
9. Niinikoski, J., Jussila, P., and Vihersaari, T. Radical mastectomy wound as a model for studies of human wound metabolism. *Am. J. Surg.* 126: 53, 1973.
10. Hunt T. K., Knighton D. R., Thakral K. K., et al. Studies on inflammation and wound healing: Angiogenesis and collagen synthesis stimulated in vivo by resident and activated wound macrophages. *Surgery* 96: 48, 1984.
11. Jensen J. A., Hunt T. K., Scheuenstuhl H., et al. Effect of lactate, pyruvate and pH on secretion of angiogenesis and

mitogenesis factors by macrophages. *Lab. Invest.* 54: 574, 1986.
12. Schultz, G., and Grant, M. Neovascular growth factors. *Eye* 5: 170, 1991.
13. Beckert, S., Hierlemann, H., Muschenborn, N., Witte, M., Ranke, M., and Coerper, S. Experimental ischemic wounds: Correlation of cell proliferation and insulin-like growth factor I expression and its modification by different local IGF-I release systems. *Wound Repair Regen.* 13: 278, 2005.
14. Knighton, D. R., Silver, I. A., and Hunt, T. K. Regulation of wound-healing angiogenesis: Effect of oxygen gradients and inspired oxygen concentration. *Surgery* 90: 262, 1981.
15. DeJong, L., and Kemp, A. Stoicheiometry and kinetics of the prolyl 4-hydroxylase partial reaction. *Biochim. Biophys. Acta* 787: 105, 1984.
16. Myllyla, R., Tuderman, L., and Kivirikko, K. I. Mechanism of the prolyl hydroxylase reaction: 2. Kinetic analysis of the reaction sequence. *Eur. J. Biochem.* 80: 349, 1977.
17. Prockop, D. J., Kivirikko, K. I., Tuderman, L., and Guzman, N. A. The biosynthesis of collagen and its disorders (first of two parts). *N. Engl. J. Med.* 301: 13, 1979.
18. Hopf, H. W., Gibson, J. J., Angeles, A. P., et al. Hyperoxia and angiogenesis. *Wound Repair Regen.* 13: 558, 2005.
19. Silver, I. A. Oxygen tension and epithelialization. In H. I. Maibach and D. T. Rovee (Eds.), *Epidermal Wound Healing.* Chicago: Year Book Medical Publishers, 1972. P. 291.
20. Medawar, P. S. The behavior of mammalian skin epithelium under strictly anaerobic conditions. *Q. J. Microsc. Sci.* 88: 27, 1947.
21. Feldmeier, J. J., Hopf, H. W., Warriner, R. A., III, Fife, C. E., Gesell, L. B., and Bennett, M. UHMS position statement: Topical oxygen for chronic wounds. *Undersea Hyperb. Med.* 32: 157, 2005.
22. O'Toole E. A., Marinkovich, M. P., Peavey, C. L., et al. Hypoxia increases human keratinocyte motility on connective tissue. *J. Clin. Invest.* 100: 2881, 1997.
23. Doughty, D. B. Preventing and managing surgical wound dehiscence. *Adv. Skin Wound Care* 18: 319, 2005.
24. Gottrup, F., Firmin, R., Rabkin, J., Halliday, B. J., and Hunt, T. K. Directly measured tissue oxygen tension and arterial oxygen tension assess tissue perfusion. *Crit. Care Med.* 15: 1030, 1987.
25. Evans, N. T. S., and Naylor, P. F. D. Steady states of oxygen tension in human dermis. *Respir. Physiol.* 2: 46, 1966.
26. Hutton, J. J., Tappel, A. L., and Udenfriend, S. Cofactor and substrate requirements of collagen proline hydroxylase. *Arch. Biochem. Biophys.* 118: 231, 1967.
27. Hohn, D. C., MacKay, R. D., Halliday, B., and Hunt, T. K. Effect of O2 tension on microbicidal function of leukocytes in wounds and in vitro. *Surg. Forum* 27: 18, 1976.
28. Jonsson, K., Hunt, T. K., and Mathes, S. J. Oxygen as an isolated variable influences resistance to infection. *Ann. Surg.* 208: 783, 1988.
29. Jensen, J. A., Goodson, W. H., Hopf, H. W., and Hunt, T. K. Cigarette smoking decreases tissue oxygen. *Arch. Surg.* 126: 1131, 1991.
30. Hopf, H. W., Hunt, T. K., West, J. M., et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch. Surg.* 132: 997; discussion 1005, 1997.
31. Jonsson, K., Jensen, J., Goodson, W., et al. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann. Surg.* 214: 605, 1991.
32. Hopf, H. W., Viele, M., Watson, J. J., et al. Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. *Arch. Surg.* 135: 1443, 2000.
33. Hopf, H., Hunt, T., and Jensen, J. Calculation of subcutaneous tissue blood flow. *Surg. Forum* 39: 33, 1988.
34. Hopf, H., and Hunt, T. Does—and if so, to what extent—normovolemic dilutional anemia influence post-operative wound healing? *Chirurg. Gastroenterologie* 8: 148, 1992.
35. Hopf, H., Viele, M., Watson, J., et al. Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. *Arch. Surg.* 135: 1443, 2000.
36. Jensen, J. A., Goodson, W. H., Vasconez, L. O., and Hunt, T. K. Wound healing in anemia. *West. J. Med.* 144: 465, 1986.
37. Sheffield, C., Sessler, D., Hopf, H., et al. Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. *Wound Repair Regen.* 4: 339, 1996.
38. Rabkin, J. M., and Hunt, T. K. Local heat increases blood flow and oxygen tension in wounds. *Arch. Surg.* 122: 221, 1987.
39. Derbyshire, D., and Smith, G. Sympathoadrenal responses to anaesthesia and surgery. *Br. J. Anaesth.* 56: 725, 1984.
40. Halter, J., Pflug, A., and Porte, D. Mechanism of plasma catecholamine increases during surgical stress in man. *J. Clin. Endocrinol. Metab.* 45: 936, 1977.
41. Kurz, A., Sessler, D., Lenhardt, R., et al. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N. Engl. J. Med.* 334: 1209, 1996.
42. Hartmann, M., Jonsson, K., and Zederfeldt, B. Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds: Randomized study in patients after major abdominal operations. *Eur. J. Surg.* 158: 521, 1992.
43. Melling, A. C., Ali, B., Scott, E. M., and Leaper, D. J. Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. *Lancet* 358: 876, 2001.
44. Akça, O., Melischek, M., Scheck, T., et al. Postoperative pain and subcutaneous oxygen tension (Letter). *Lancet* 354: 41, 1999.
45. Rojas, I. G., Padgett, D. A., Sheridan, J. F., and Marucha, P. T. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. *Brain Behav. Immun.* 16: 74, 2002.
46. Horan, M. P., Quan, N., Subramanian, S. V., Strauch, A. R., Gajendrareddy, P. K., and Marucha, P. T. Impaired wound contraction and delayed myofibroblast differentiation in restraint-stressed mice. *Brain Behav. Immun.* 19: 207, 2005.
47. Greif, R., Akca, O., Horn, E. P., Kurz, A., and Sessler, D. I. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. *N. Engl. J. Med.* 342: 161, 2000.
48. Belda, F. J., Aguilera, L., Garcia de la Asuncion, J., et al. Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. *J.A.M.A.* 294: 2035, 2005.
49. Pryor, K. O., Fahey, T. J., III, Lien, C. A., and Goldstein, P. A. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *J.A.M.A.* 291: 79, 2004.
50. Classen, D., Evans, R., Pestotnik, S., Horn, S., Menlove, R., and Burke, J. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. *N. Engl. J. Med.* 326: 281, 1992.
51. Knighton, D. R., Halliday, B., and Hunt, T. K. Oxygen as an antibiotic: A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. *Arch. Surg.* 121: 191, 1986.
52. Fawcett, A., Shembekar, M., Church, J., Vashisht, R., Springall, R., and Nott, D. Smoking, hypertension, and colonic anastomotic healing: A combined clinical and histopathological study. *Gut* 38: 714, 1996.

53. Kaye, K. S., Sands, K., Donahue, J. G., Chan, K. A., Fishman, P., and Platt, R. Preoperative drug dispensing as predictor of surgical site infection. *Emerging Infect. Dis.* 7: 57, 2001.
54. Haydock D., and Hill G. Improved wound healing response in surgical patients receiving intravenous nutrition. *Br. J. Surg.* 74: 320, 1987.
55. Goodson, W. D., Lopez, S. A., Jensen, J. A., West, J., Granja, M. L., and Chavez, E. J. The influence of a brief preoperative illness on postoperative healing. *Ann. Surg.* 205: 250, 1987.
56. Barbul, A., Lazarou, S., Efron, D., et al. Arginine enhances wound healing and lymphocyte immune response in humans. *Surgery* 108: 331, 1990.
57. Patel, G. K. The role of nutrition in the management of lower extremity wounds. *Int. J. Low Extrem. Wounds* 4: 12, 2005.
58. Hunt, T., Ehrlich, H., Garcia, J., and Dunphy, J. Effect of vitamin A on reversing the inhibitor effect of cortisone on healing of open wounds in animals and man. *Ann. Surg.* 170: 633, 1969.
59. Wicke, C., Halliday, B., Allen, D., et al. Effects of steroids and retinoids on wound healing. *Arch. Surg.* 135: 1265, 2000.
60. Seifter, E., Rettura, G., Padawer, J., et al. Impaired wound healing in streptozotocin diabetes: Prevention by supplemental vitamin A. *Ann. Surg.* 194: 42,1981.
61. Winsey, K., Simon, R. J., Levenson, S. M., Seifter, E., and Demetriou, A. A. Effect of supplemental vitamin A on colon anastomotic healing in rats given preoperative irradiation. *Am. J. Surg.* 153: 153, 1987.
62. Hunt, T., and Hopf, H. Nutrition in wound healing. In J. Fischer (Ed.), *Nutrition and Metabolism in the Surgical Patient*, 2nd Ed. Boston: Little, Brown, 1996. Pp. 423–441.
63. Haley, R. W., Culver, D. H., Morgan, W. M., White, J. W., Emori, T. G., and Hooton, T. M. Identifying patients at high risk of surgical wound infection: A simple multivariate index of patient susceptibility and wound contamination. *Am. J. Epidemiol.* 121: 206, 1985.
64. Culver, D., Horan, T., Gaynes, R., et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. *Am. J. Med.* 91: 152S, 1991.
65. Miles, A., Miles, E., and Burke, J. The value and duration of defence reactions of the skin to the primary lodgment of bacteria. *Br. J. Exp. Pathol.* 38: 79, 1957.
66. Nichols, R. L., Condon, R. E., and Barie, P. S. Antibiotic prophylaxis in surgery: 2005 and beyond. *Surg. Infect. (Larchmt.) Fall.* 6: 349, 2005.
67. Bratzler, D. W., and Houck, P. M. Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. *Clin. Infect. Dis.* 38: 1706, 2004.
68. Burke J. P. Maximizing appropriate antibiotic prophylaxis for surgical patients: An update from LDS Hospital, Salt Lake City. *Clin. Infect. Dis.* 33 (Suppl. 2): S78, 2001.
69. Scher, K. Studies on the duration of antibiotic administration for surgical prophylaxis. *Am. Surg.* 63: 59, 1997.
70. Mathes, S. J., Steinwald, P. M., Foster, R. D., Hoffman, W. Y., and Anthony, J. P. Complex abdominal wall reconstruction: A comparison of flap and mesh closure. *Ann. Surg.* 232: 586, 2000.
71. Matsukawa, T., Sessler, D., Sessler, A., et al. Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 82: 662, 1995.
72. West, J., Hopf, H., Sessler, D., and Hunt, T. The effect of rapid postoperative rewarming on tissue oxygen. *Wound Repair Regen.* 1: 93, 1993.
73. Kurz, A., Kurz, M., Poeschl, G., Faryniak, B., Redl, G., and Hackl, W. Forced-air warming maintains intraoperative normothermia better than circulating water mattresses. *Anesth. Analg.* 77: 89, 1993.
74. Arkilic, C. F., Taguchi, A., Sharma, N., et al. Supplemental perioperative fluid administration increases tissue oxygen pressure. *Surgery* 133: 49, 2003.
75. Gabrielli, F., Potenza, C., Puddu, P., Sera, F., Masini, C., and Abeni, D. Suture materials and other factors associated with tissue reactivity, infection, and wound dehiscence among plastic surgery outpatients. *Plast. Reconstr. Surg.* 107: 38, 2001.
76. Plattner, O., Akca, O., Herbst, F., et al. The influence of 2 surgical bandage systems on wound tissue oxygen tension. *Arch. Surg.* 135: 818, 2000.
77. Verrier, E., Bossart, K., and Heer, F. Reduction of infection rates in abdominal incisions by delayed wound closure techniques. *Am. J. Surg.* 138: 22, 1979.
78. Jonsson, K., Jensen, J. A., Goodson, W. H., West, J. M., and Hunt, T. K. Assessment of perfusion in postoperative patients using tissue oxygen measurements. *Br. J. Surg.* 74: 263, 1987.
79. Jensen, J. A., Goodson, W. H., III, Omachi, R. S., Lindenfeld, S. M., and Hunt, T. K. Subcutaneous tissue oxygen tension falls during hemodialysis. *Surgery* 101: 416, 1987.
80. Mangano, D., Layug, E., Wallace, A., and Tateo, I. Group TMSoPIR: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery *N. Engl. J. Med.* 335: 1713, 1996.
81. Stuhmeier, K., Mainzer, B., Cierpka, J., Sandmann, W., and Tarnow, K. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. *Anesthesiology* 85: 706, 1996.
82. Mangano, D., Martin, E., Motsch, J., et al. Perioperative sympatholysis: Beneficial effects of the alpha-2-adrenoreceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. *Anesthesiology* 86: 346, 1997.
83. Wallace, A. W., Galindez, D., Salahieh, A., et al. Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. *Anesthesiology* 101: 284, 2004.
84. Hopf, H., West, J., and Hunt, T. Clonidine increases tissue oxygen in patients with local tissue hypoxia in non-healing wounds. *Wound Repair Regen.* 4: A129, 1996.
85. Wisner, D. A stepwise logistic regression analysis of factors affecting morbidity and mortality after thoracic trauma: Effect of epidural analgesia. *J. Trauma* 30: 799, 1990.
86. Owen, H., McMillan, V., and Rogowski, D. Postoperative pain therapy: A survey of patients' expectations and their experiences. *Pain* 41: 303, 1990.
87. Donovan, M., Dillon, P., and McGuire, L. Incidence and characteristics of pain in a sample of medical-surgical inpatients. *Pain* 30: 69, 1987.
88. Fuchs, U., Zittermann, A., Stuettgen, B., Groening, A., Minami, K., and Koerfer, R. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: A retrospective analysis. *Ann. Thorac. Surg.* 79: 526, 2005.
89. Hunt, T. K., and Hopf, H. W. Wound healing and wound infection: What surgeons and anesthesiologists can do. *Surg. Clin. North Am.* 77: 587, 1997.