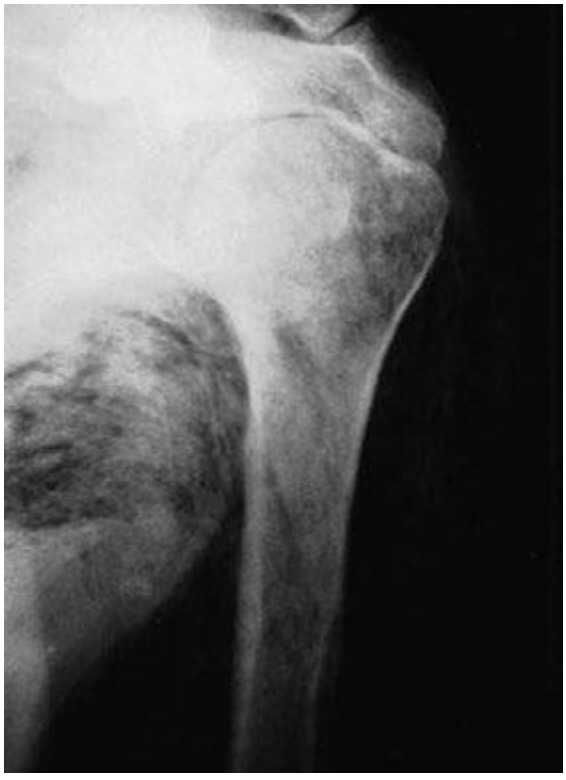

FIGURE 179-2 Radiograph of patient with spontaneous gas gangrene due to *C. septicum*, demonstrating gas in the affected arm and shoulder.

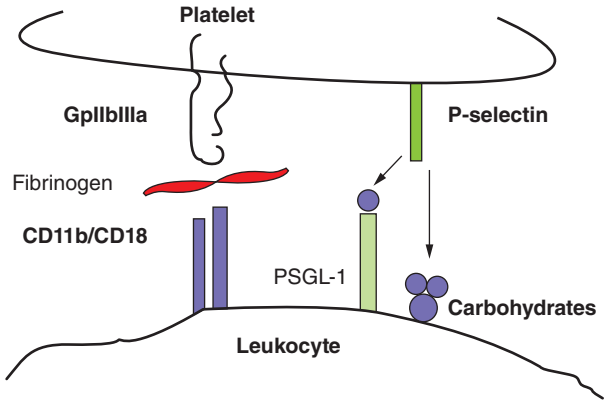

FIGURE 179-3 Schematic illustration of the molecular mechanisms of *C. perfringens* α toxin–induced platelet/neutrophil aggregates. Homotypic aggregates of platelets (not shown) and heterotypic aggregates of platelets and leukocytes are due to α toxin–induced activation of the platelet fibrinogen receptor gpIIb/IIIa and upregulation of leukocyte CD11b/CD18. Binding of fibrinogen (*red*) bridges the connection between these adhesion molecules on adjacent cells. An auxiliary role for α toxin–induced upregulation of platelet P-selectin and its binding to leukocyte P-selectin glycoprotein ligand 1 (PSGL-1) or other leukocyte surface carbohydrates also has been demonstrated.

environment for growth of these species. These conditions are not strictly required for the more aerotolerant species such as *C. septicum* and *C. tertium*, which can seed normal tissues from gastrointestinal lesions. Once introduced into an appropriate niche, the organisms proliferate locally and elaborate exotoxins.

The major *C. perfringens* extracellular toxins implicated in gas gangrene are α toxin and θ toxin. A lethal hemolysin that has both phospholipase C and sphingomyelinase activities, α toxin has been implicated as the major virulence factor of *C. perfringens*: immunization of mice with the C-terminal domain of α toxin provides protection against lethal challenge with *C. perfringens*, and isogenic α toxin–deficient mutant strains of *C. perfringens* are not lethal in a murine model of gas gangrene. It has been shown in experimental models that the severe pain, rapid progression, marked tissue destruction, and absence of neutrophils in *C. perfringens* gas gangrene are attributable in large part to α toxin–induced occlusion of blood vessels by heterotypic aggregates of platelets and neutrophils. The formation of these aggregates, which occurs within minutes, is largely mediated by α toxin's ability to activate the platelet adhesion molecule gpIIb/IIIa (Fig. 179-3); the implication is that platelet glycoprotein inhibitors (e.g., eptifibatide, abciximab) may be therapeutic for maintaining tissue blood flow.

C. perfringens θ toxin (*perfringolysin*) is a member of the thiol-activated cytolysin family known as cholesterol-dependent cytolysins, which includes streptolysin O from group A *Streptococcus*, pneumolysin from *Streptococcus pneumoniae*, and several other toxins. Cholesterol-dependent cytolysins bind as oligomers to cholesterol in host cell membranes. At high concentrations, these toxins form ring-like pores resulting in cell lysis. At sublytic concentrations, θ toxin hyperactivates phagocytes and vascular endothelial cells.

Cardiovascular collapse and end-organ failure occur late in the course of *C. perfringens* gas gangrene and are largely attributable to both direct and indirect effects of α and θ toxins. In experimental models, θ toxin causes markedly reduced systemic vascular resistance but increased cardiac output (i.e., "warm shock"), probably via induction of endogenous mediators (e.g., prostacyclin, platelet-activating factor) that cause vasodilation. This effect is similar to that observed in gram-negative sepsis. In sharp contrast, α toxin directly suppresses myocardial contractility; the consequence is profound hypotension due to a sudden reduction in cardiac output. The roles of other endogenous mediators, such as cytokines (e.g., tumor necrosis factor, interleukin 1, interleukin 6) and vasodilators (e.g., bradykinin) have not been fully elucidated.

C. septicum produces four main toxins—α toxin (lethal, hemolytic, necrotizing activity), β toxin (DNase), γ toxin (hyaluronidase), and Δ toxin (septicolysin, an oxygen-labile hemolysin)—as well as a protease and a neuraminidase. Unlike the α toxin of *C. perfringens*, that of *C. septicum* does not possess phospholipase activity. The mechanisms remain to be fully elucidated, but it is likely that each of these toxins contributes uniquely to *C. septicum* gas gangrene.

TREATMENT GAS GANGRENE

Patients with suspected gas gangrene (either traumatic or spontaneous) should undergo prompt surgical inspection of the infected site. Direct examination of a Gram-stained smear of the involved tissues is of major importance. Characteristic histologic findings in clostridial gas gangrene include widespread tissue destruction, a paucity of leukocytes in infected tissues in conjunction with an accumulation of leukocytes in adjacent vessels (Fig. 179-4), and the presence of gram-positive rods (with or without spores). CT and MRI are invaluable for determining whether the infection is localized or is spreading along fascial planes, and needle aspiration or punch biopsy may provide an etiologic diagnosis in at least 20% of cases. However, these techniques should not replace surgical exploration, Gram's staining, and histopathologic examination. When spontaneous gas gangrene is suspected, blood should be cultured since bacteremia usually precedes cutaneous manifestations by several hours.

For patients with evidence of clostridial gas gangrene, thorough emergent surgical debridement is of extreme importance. All devitalized tissue should be widely resected back to healthy viable muscle and skin so as to remove conditions that allow anaerobic organisms to continue proliferating. Closure of traumatic wounds or compound fractures should be delayed for 5–6 days until it is certain that these sites are free of infection.