Biomedical Science

Mechanisms and Consequences of Leukocyte-Endothelial Interaction

JOHN M. HARLAN, MD, NICHOLAS B. VEDDER, MD, ROBERT K. WINN, PhD, *and* CHARLES L. RICE, MD, *Seattle, Washington*

Presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 6-7, 1991.

Leukocyte adhesion to endothelium is a critical event in host defense against microorganisms and in the repair of tissue damage. Under some circumstances, however, altered leukocyte-endothelial interactions may contribute to the pathogenesis of inflammatory and immune diseases. In a number of experimental models, the inhibition of leukocyte adherence to endothelium substantially reduces vascular and tissue injury. Antiadhesion therapy may represent a novel approach to the treatment of a wide spectrum of clinical disorders.

(Harlan JM, Vedder NB, Winn RK, Rice CL: Mechanisms and consequences of leukocyte-endothelial interaction. West J Med 1991 Oct; 155:365-369)

A new approach to the treatment of inflammatory and immune disorders has recently emerged from clinical observations, cell and molecular biology studies, and investigations in animal models of disease. The focus of this approach is the interaction of circulating leukocytes with vascular endothelium.[1] In response to diverse extravascular stimuli such as infection, foreign antigen, or tissue damage, signals are generated that activate either the leukocyte or the endothelial cell. As a consequence of activation, one or both cell types become adhesive for the other, leading to increased leukocyte adherence to endothelium at the site of inflammation or immune reaction. The adherent leukocyte then moves across the vessel wall to extravascular sites, diapedesing between endothelial cells and migrating through the subendothelial matrix to tissue. There it participates in inflammatory or immune reactions. Because the leukocyte must adhere to the endothelium to emigrate to the extravascular site, considerable attention has been focused on the leukocyte and endothelial cell surface molecules that mediate this adhesive interaction.

In the past ten years, more than a dozen proteins involved in the adherence of leukocytes to endothelium have been functionally and immunochemically identified and molecularly cloned.[2,3] Leukocyte-endothelial adhesion molecules can be divided into two categories: integrin receptors on leukocytes that interact with ligands on the endothelial cell and that are members of the immunoglobulin gene superfamily, and a new class of proteins, LEC-CAMs or "selectins," that recognize specific carbohydrate counterstructures on the endothelial cell or on the leukocyte. In this brief review we will focus on the leukocyte integrin receptor that mediates neutrophil adherence to endothelium.

As with many other problems in biology, important insights into the molecular basis of leukocyte adherence to endothelium have come from studies of a genetic deficiency syndrome. Leukocyte adhesion deficiency or leukocyte-cell adhesion molecule-deficiency syndrome results from a partial or complete deficiency of the leukocyte adhesion receptor complex, CD11/CD18 (CD refers to cluster differentiation).[4-6] The CD11/CD18 complex consists of three heterodimeric subunits. Each subunit contains a common β-chain, designated CD18, and a distinct α-chain, designated CD11a, CD11b, or CD11c. The heterodimeric subunits are also commonly known as LFA-1 (CD11a/CD18); Mac-1 or Mo1 (CD11b/CD18), which is also the complement receptor type 3 (CR3); and p150,95 (CD11c/CD18). LFA-1 is found on all leukocytes, whereas Mac-1 and p150,95 are restricted to phagocytes and natural killer cells (Figure 1). The three α-chains and the common β-chain have been molecularly cloned by a number of groups and shown to be members of the integrin superfamily of adhesion receptors (reviewed by Arnaout and Larson and Springer[6,7]). The CD11/CD18 complex makes up the β_2 subclass of this family and is found only on leukocytes.

The CD11/CD18-deficiency syndrome is inherited in an autosomal recessive manner; heterozygotes have no signifi-

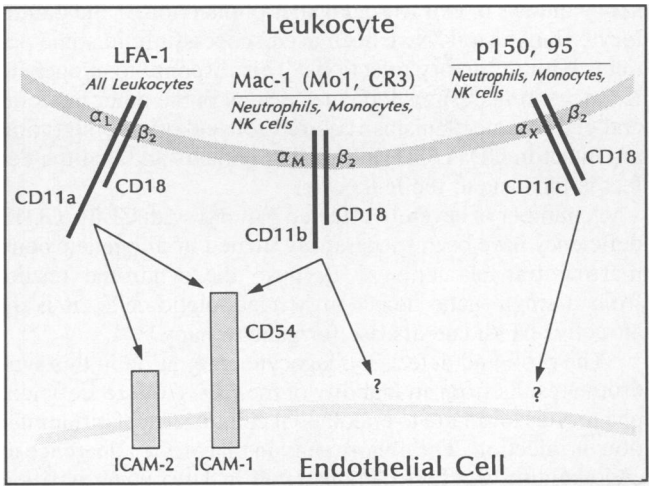

Figure 1.—The leukocyte CD11/CD18 complex and its endothelial ligands, intercellular adhesion molecules-1 and -2 (ICAM-1, ICAM-2), are shown. NK = natural killer

From the Department of Medicine, Division of Hematology (Dr Harlan), and the Department of Surgery (Drs Vedder, Winn, and Rice), University of Washington School of Medicine, Seattle.

Dr Harlan receives research funding in the field of cell adhesion from Cytel Corporation, La Jolla, California.

Reprint requests to John M. Harlan, MD, Division of Hematology RM-10, University of Washington, Seattle, WA 98195.

cant clinical manifestations. The molecular basis of the CD11/CD18-deficiency syndrome has been shown to result from heterogeneous mutations in the common β-chain.[8] A complete failure to synthesize any β-chain or the synthesis of only abnormal β-chain does not allow association of the three α-chains with the β-chain in heterodimers and thereby prevents their insertion into the plasma membrane. Such persons have a complete absence of surface membrane CD11/CD18 and exhibit a severe phenotype. Persons with mutations allowing the synthesis of some functional β-chain have a partial deficiency and mild to moderate phenotype. Interestingly, the CD11/CD18-deficiency syndrome has been reported as a granulocytopathy syndrome in a dog and in Holstein cows.[9,10]

The clinical manifestations of the CD11/CD18-deficiency syndrome have been reviewed in detail.[4-6] The CD11/CD18-deficient patients frequently present with delayed separation of the umbilical cord at birth, presumably resulting from impaired wound healing. Severely affected patients suffer from recurrent, sometimes life-threatening bacterial infections throughout life. The infections often begin at skin or mucous membranes and may progress to overt sepsis. The most striking feature of CD11/CD18 deficiency is the absence of neutrophils and monocytes at the sites of infection—that is, the patients have a failure to suppurate. Despite this profound defect in phagocyte migration, CD11/CD18-deficient patients have chronic neutrophilic leukocytosis with leukocyte counts as high as 100×10^9 per liter (100,000 per μl) during episodes of acute infection. Presumably, the signals required to mobilize neutrophils from stores in the bone marrow, such as colony-stimulating factors, are intact, and the CD11/CD18-deficient cells accumulate in the circulation because of their inability to migrate.

All of the major clinical manifestations of CD11/CD18-deficiency syndrome can be ascribed to the defect in phagocyte migration. This defect is most dramatically evidenced by the absence of pus at the sites of infection. Also, the patients' neutrophils fail to migrate normally to skin chambers or skin windows. Transfused allogenic neutrophils do migrate to skin windows or extravascular sites of infection,[11] and granulocyte transfusions have been used successfully in some patients with refractory infections. This response to allogeneic leukocyte transfusions indicates that all of the other humoral and cellular mechanisms required for leukocyte emigration are intact in CD11/CD18-deficient patients and that the defect is intrinsic to the leukocyte.

A number of severely affected patients with CD11/CD18 deficiency have been successfully treated by allogeneic bone marrow transplantation.[12] Because the syndrome results from a single gene defect in hematopoietic cells, it is an attractive candidate disease for gene therapy.[13,14]

The profound defect in phagocyte emigration in this syndrome results from an inability of the CD11/CD18-deficient phagocytes to adhere to endothelial cells at sites of inflammation or infection. The abnormality in phagocyte adherence to endothelium was first demonstrated in vitro using purified neutrophils isolated from an affected patient and endothelial cells from cultured human umbilical vein.[15] Normal neutrophils have a low basal adherence to cultured endothelium but can be stimulated to increase binding markedly with various activating agents such as bacterial chemotactic peptide, platelet-activating factor, tumor necrosis factor, interleukin-8, or complement fragment C5a. CD11/CD18-deficient neutrophils fail to augment adherence when stimulated, and this defect in stimulated adherence is reproduced in normal neutrophils by monoclonal antibodies directed at functional epitopes on the α (CD11b)- or β (CD18)-chains of the Mac-1 subunit and to a lesser extent with monoclonal antibodies to α-chain (CD11a) of the LFA-1 subunit. The inability of CD11/CD18-deficient neutrophils to adhere to endothelium when stimulated also results in an inability to migrate across the endothelial monolayer in response to chemotactic stimuli.[15]

The CD11/CD18 complex is involved not only in the heterotypic adhesion of neutrophils to other cells such as endothelial cells but also in the homotypic adhesion or aggregation of neutrophils. When neutrophils have exposure to a wide variety of stimuli, they rapidly form homotypic aggregates. This aggregation response is completely absent in CD11/CD18-deficient neutrophils and is abolished in normal neutrophils by monoclonal antibodies to CD11b or CD18.[16]

The availability of blocking monoclonal antibodies that cross-react with CD11b or CD18 in other species has allowed an investigation of the role of the CD11/CD18 complex in the in vivo interaction of neutrophils and endothelium. Administering CD11b or CD18 monoclonal antibodies has been shown to inhibit neutrophil migration to experimentally induced sites of inflammation in the skin, peritoneum, lungs, joints, and meninges.[2] The CD11b or CD18 monoclonal antibodies do not reduce the circulating neutrophil count but, in fact, produce leukocytosis similar to that observed in patients with CD11/CD18 deficiency. Studies using intravital microscopy have confirmed that the blockade in neutrophil migration produced by these CD11b or CD18 monoclonal antibodies is due to inhibited adherence of leukocytes to endothelium. Superfusion of the microcirculation with a chemoattractant produces leukocyte adherence to vessel walls, intravascular aggregation of leukocytes, and leukocyte diapedesis across vessel walls to extravascular tissue. Pretreatment with a CD18 monoclonal antibody completely abolishes aggregation and sticking.[17] Of interest, although the CD18 monoclonal antibody prevented "sticking," the leukocytes continued to "roll" along the vessel wall. The rolling of leukocytes along the vessel thus appears to be mediated by adhesion molecules other than the CD11/CD18 complex.

Two of the endothelial counterstructures for the CD11/CD18 complex have been identified as intercellular adhesion molecules 1 and 2 (ICAM-1, CD54; ICAM-2) (Figure 1).[18,19] ICAM-1 and ICAM-2 are both members of the immunoglobulin superfamily of proteins that interact with the LFA-1 subunit (CD11a/CD18).[20] ICAM-1 also binds the Mac-1 subunit (CD11b/CD18).[20] There appear to be other counterstructures for Mac-1 and p150,95 (CD11c/CD18) on endothelium that have not yet been identified.

In pronounced contrast to neutrophils, lymphocyte traffic in CD11/CD18-deficient patients appears to be normal, although their lymphocytes also lack CD11/CD18. Biopsy specimens of tissue at sites of inflammation or immune reaction show an infiltration of lymphocytes, occasional eosinophils, and rare monocytes but no neutrophils.[4,11] Moreover, cell-mediated immune responses are largely intact as the patients show delayed-type hypersensitivity reactions and do not usually suffer from viral or opportunistic infections. Obviously, lymphocytes, monocytes, eosinophils, and other

cell types must possess an adhesion receptor(s) other than CD11/CD18 that is capable of mediating binding to endothelium. Selectin molecules may play an important role in this CD11/CD18-independent mechanism of binding. The β_1 integrin receptor, very-late-activation antigen-4 (VLA-4; CD49d/CD29), however, is the most likely candidate for this alternate pathway of adhesion and emigration. VLA-4 binds to vascular cell adhesion molecule-1 (VCAM-1), a cytokine-induced endothelial protein that is a member of the immunoglobulin superfamily.[21-23] Most important, VLA-4 is expressed on all leukocyte classes except neutrophils. Thus, the CD11/CD18-deficiency syndrome with its profound defect in neutrophil adhesion and migration likely occurs because neutrophils uniquely lack this alternate integrin receptor.

It is clear from clinical manifestations of CD11/CD18 deficiency that neutrophil adherence to endothelium is a critical event in host defense. Under some circumstances, however, neutrophil adhesion to endothelium may have deleterious consequences for the host. Exaggerated or unregulated neutrophil adhesion may lead to endothelial damage by toxic products, such as proteases and oxidants, released by the adherent neutrophil. Altered neutrophil-endothelial interactions have been implicated in the pathogenesis of vascular and tissue injury in a wide variety of clinical disorders including sepsis, inflammatory skin diseases, the adult respiratory distress syndrome, vasculitides, and some forms of glomerulonephritis.[24]

Neutrophil adhesion may play a particularly important role in diverse disorders associated with ischemia and reperfusion, including myocardial infarction, stroke, shock, organ transplantation, limb replantation, burns, and crush injuries. With prolonged ischemia there is damage to tissue from anoxia, but, paradoxically, further injury may occur after reperfusion. At least in some settings, this reperfusion injury appears to involve an inflammatory response.[25] Clearly the inflammatory system evolved long before reperfusion of ischemic organs was possible, so reperfusion injury probably represents an "accidental" triggering of the inflammatory response, not a mechanism of host defense and repair. The precise signals, such as oxidants, complement components, or cytokines, that trigger the inflammatory response during reperfusion have not been identified and may vary with the particular organ or disorder. The activation of leukocytes and endothelial cells during reperfusion results in neutrophil adhesion in capillaries producing plugging and further ischemia, or neutrophil adhesion to endothelium leading to the emigration of neutrophils with local edema formation, hemorrhage, and thrombosis. Because the CD11/CD18 complex is critically involved in these homotypic and heterotypic adhesive interactions of neutrophils, there is an opportunity to intervene therapeutically with blocking monoclonal antibodies directed at CD11b or CD18 (Figure 2).

Vedder and associates tested this novel approach in a rabbit ear model of isolated tissue ischemia-reperfusion.[26] They observed that the inhibition of leukocyte adherence with the CD18 monoclonal antibody 60.3—developed by Beatty and colleagues[27]—greatly attenuated neutrophil accumulation and associated endothelial and tissue injury after ten hours of warm ischemia followed by reperfusion. Furthermore, they found that this protection was the same whether the antibody was administered after ischemia occurred, but before reperfusion, or when administered before ischemia. These results indicate that leukocytes are important mediators of ischemia-reperfusion injury, that the leukocyte-mediated injury is in fact a reperfusion injury, and that it can be substantially attenuated by a CD18 monoclonal antibody administered at the time of reperfusion.

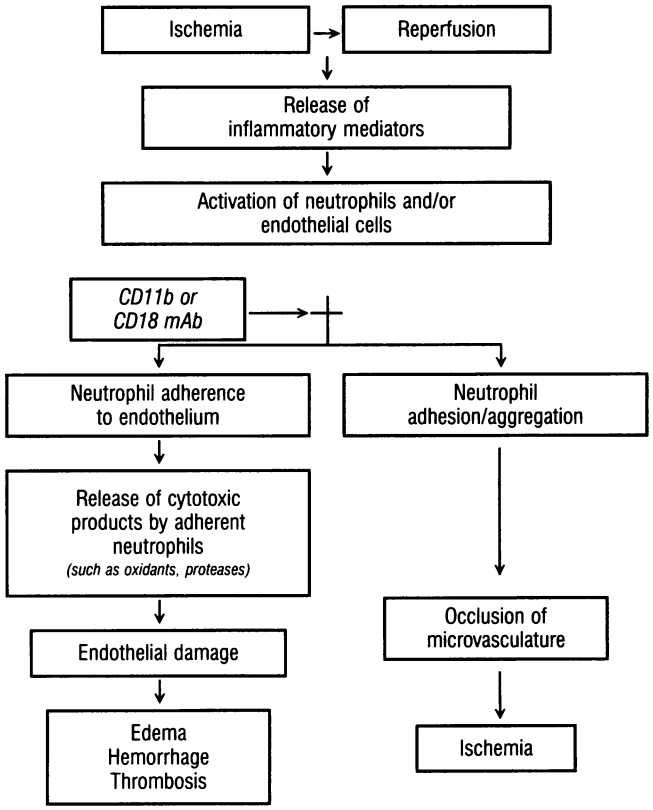

Figure 2.—The possible mechanism of action of CD11b or CD18 monoclonal antibody (mAb) is shown in preventing vascular and tissue injury after ischemia and reperfusion.

This approach was further tested in an animal model of hemorrhagic shock and resuscitation that may be relevant to the clinical syndrome of multiple organ failure. This syndrome is characterized by cardiovascular, pulmonary, central nervous system, hepatic, gastrointestinal, and renal dysfunction along with signs of generalized inflammation.[28,29] Vedder and colleagues hypothesized that shock (ischemia) followed by resuscitation (reperfusion) led to neutrophil adhesion in the microcirculation and the subsequent development of multiple organ failure. Administering the CD18 monoclonal antibody 60.3 before shock[30] or at the time of resuscitation[31] dramatically reduced the amount of vascular and tissue injury and improved survival in a rabbit model. These results were recently confirmed in a primate model in which a CD18 monoclonal antibody was administered at the time of resuscitation from hemorrhagic shock.[32] In control animals diffuse vascular injury developed, manifested by the capillary leak syndrome, requiring large volumes of fluid to maintain cardiac output. Visceral injury also developed in control animals in the form of gastritis observed by endoscopy. In contrast, animals treated with the CD18 monoclonal antibody required no fluids above maintenance to maintain cardiac output, and gastritis did not develop. Two of five control animals died, whereas all animals treated with monoclonal antibody 60.3 survived (Table 1).[32]

TABLE 1.—*Effect of CD18 Monoclonal Antibody Use in Hemorrhagic Shock**

Clinical Effect	Animals: Control (n = 5)	Animals: 60.3-Treated (n = 5)
Fluid requirements†	259.8±225.7	9.6±8.8
Gastritis‡	5	0
Death, No.	2	0

*The CD18 monoclonal antibody 60.3 reduced vascular and tissue injury following hemorrhagic shock and resuscitation in primates (from Mileski et al[32]).
†Unit is milliliter per kilogram above maintenance required to maintain cardiac output over the first 24 hours.
‡Number of animals with the finding, as assessed by endoscopy.

These studies in the animal models show that CD18 monoclonal antibodies may prevent vascular and tissue damage by the inhibition of neutrophil adhesion after the generalized ischemia and reperfusion associated with shock and resuscitation. They also suggest that a similar approach may prevent or reduce the severity of multiple organ failure syndrome and prolong survival in trauma patients.

As dramatically shown by CD11/CD18-deficient patients, neutrophil adhesion to endothelium is necessary for host defense against bacterial infection at extravascular sites, raising the concern that even a transient inhibition of neutrophil adhesion might notably increase the susceptibility to and severity of bacterial infection. This possibility was examined in two models of infection in rabbits. The use of a CD18 monoclonal antibody did not increase mortality or infectious complications in animals with bacterial peritonitis,[33] and its use did not increase abscess formation at clinically relevant inocula of staphylococcal organisms in the skin.[34] These studies provide some reassurance that it may be safe to inhibit completely neutrophil adhesion for a limited period, even in trauma patients who are at risk of infection.

"Antiadhesion" therapy with monoclonal antibodies to the CD11/CD18 complex or its ligand ICAM-1 has been tested in a number of other models of ischemia-reperfusion and inflammatory or immune disorders (Table 2).[27,30-32,35-42] Other adhesion receptor-ligand interactions such as VLA-4 or VCAM-1 and the selectins are also possible targets for antiadhesion therapy. Possible therapeutic agents include murine or "humanized" monoclonal antibodies, peptides, soluble receptors, or small molecules (such as carbohydrates) that inhibit receptor-ligand interactions. Alternatively, drugs may be developed that disrupt the signal transduction pathways that are involved in the induction or activation of adhesion molecules.

TABLE 2.—*Antiadhesion Therapy in Experimental Models*

Model (Animal)	Adhesion Protein	Reference
Reperfusion injury		
Intestine (cat)	CD18	Hernandez et al, 1987[35]
Ear (rabbit)	CD18	Beatty et al, 1983[27]
Lung (rabbit)	CD18	Horgan et al, 1990[36]
Skeletal muscle (dog)	CD18	Carden et al, 1990[37]
Hemorrhagic shock (rabbit, primate)	CD18	Vedder et al, 1988[30]; Vedder et al, 1989[31]; Mileski et al, 1990[32]
Cerebral edema in bacterial meningitis (rabbit)	CD18	Tuomanen et al, 1989[38]
Myocardial infarction (dog)	CD11b	Simpson et al, 1990[39]
Autoimmune diabetes (mouse)	CD11b	Hutchings et al, 1990[40]
Allergic asthma (primate)	ICAM-1	Wegner et al, 1990[41]
Renal allograft rejection (primate)	ICAM-1	Cosimi et al, 1990[42]

In summary, there has been dramatic recent progress in our understanding of the cell and molecular biology, physiology, and clinical relevance of leukocyte-endothelial interactions. These insights may lead to the development of new therapies for a variety of human diseases.

REFERENCES

1. Harlan JM: Leukocyte-endothelial interactions. Blood 1985; 65:513-525
2. Carlos TM, Harlan JM: Membrane proteins involved in phagocyte adherence to endothelium. Immunol Rev 1990; 114:5-28
3. Springer TA: Adhesion receptors of the immune system. Nature 1990; 346: 425-434
4. Anderson DC, Schmalstieg FC, Finegold MJ, et al: The severe and moderate phenotypes of heritable Mac-1, LFA-1 deficiency: Their quantitative definition and relation to leukocyte dysfunction and clinical features. J Infect Dis 1985; 152:668-689
5. Todd RF III, Freyer DR: The CD11/CD18 leukocyte glycoprotein deficiency. Hematol Oncol Clin North Am 1988; 2:13-31
6. Arnaout MA: Leukocyte adhesion molecules deficiency: Its structural basis, pathophysiology and implications for modulating the inflammatory response. Immunol Rev 1990; 114:145-180
7. Larson RS, Springer TA: Structure and function of leukocyte integrins. Immunol Rev 1990; 114:179-217
8. Kishimoto TK, Hollander N, Roberts TM, Anderson DC, Springer TA: Heterogeneous mutations in the β subunit common to the LFA-1, Mac-1, and p150,95 glycoproteins cause leukocyte adhesion deficiency. Cell 1987; 50:193-202
9. Giger U, Boxer LA, Simpson PJ, Lucchesi BR, Todd RF III: Deficiency of leukocyte surface glycoproteins Mo1, LFA-1, and Leu M5 in a dog with recurrent bacterial infections: An animal model. Blood 1987; 69:1622-1630
10. Kehrli ME, Schmalstieg FC, Anderson DC, et al: Molecular definition of the bovine granulocytopathy syndrome: Identification of deficiency of the Mac-1 (CD11b/CD18) glycoprotein. Am J Vet Res 1990; 51:1826-1836
11. Bowen TJ, Ochs HD, Altman LC, et al: Severe recurrent bacterial infections associated with defective adherence and chemotaxis in two patients with neutrophils deficient in a cell-associated glycoprotein. J Pediatr 1982; 101:932-940
12. Le Deist F, Blanche S, Keable H, et al: Successful HLA nonidentical bone marrow transplantation in three patients with the leukocyte adhesion deficiency. Blood 1989; 74:512-516
13. Wilson JM, Ping AJ, Krauss JC, et al: Correction of CD18-deficient lymphocytes by retrovirus-mediated gene transfer. Science 1990; 248:1413-1416
14. Back AL, Kwok WW, Adam M, Collins SJ, Hickstein DD: Retroviral-mediated gene transfer of the leukocyte integrin CD18 subunit. Biochem Biophys Res Commun 1990; 171:787-795
15. Harlan JM, Killen PD, Senecal FM, et al: The role of neutrophil membrane glycoprotein GP-150 in neutrophil adherence to endothelium in vitro. Blood 1985; 66:167-178
16. Schwartz BR, Ochs HD, Beatty PG, Harlan JM: A monoclonal antibody-defined membrane antigen complex is required for neutrophil-neutrophil aggregation. Blood 1985; 65:1553-1556
17. Arfors KE, Lundberg C, Lindbom L, Lundberg K, Beatty PG, Harlan JM: A monoclonal antibody to the membrane glycoprotein complex CD18 inhibits polymorphonuclear leukocyte accumulation and plasma leakage in vivo. Blood 1987; 69: 338-340
18. Staunton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA: Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell 1988; 52:925-933
19. Staunton DE, Dustin ML, Springer TA: Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 1989; 339:61-64
20. Smith CW, Marlin SD, Rothlein R, Toman C, Anderson DC: Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils in vitro. J Clin Invest 1989; 83:2008-2017
21. Osborn L, Hession C, Tizard T, et al: Direct expression cloning of vascular cell adhesion molecule-1 (VCAM-1), a cytokine-induced endothelial protein that binds to lymphocytes. Cell 1989; 59:1203-1211
22. Elices MJ, Osborn L, Takada Y, et al: VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4/fibronectin binding site. Cell 1990; 60:577-584
23. Schwartz BR, Wayner LA, Carlos TM, Ochs HD, Harlan JM: Identification of surface proteins mediating adherence of CD11/CD18-deficient lymphoblastoid cells to cultured human endothelium. J Clin Invest 1990; 85:2019-2022
24. Harlan JM: Neutrophil-mediated vascular injury. Acta Med Scand 1987; 715:123-129
25. Granger DN, Benoit JN, Suzuki M, Grisham MB: Leukocyte adherence to venular endothelium during ischemia-reperfusion. Am J Physiol 1989; 257:G683-G688
26. Vedder NB, Winn RK, Rice CL, Chi EY, Arfors KE, Harlan JM: Inhibition of leukocyte adherence by anti-CD18 monoclonal antibody attenuates reperfusion injury in the rabbit ear. Proc Natl Acad Sci USA 1990; 87:2643-2646
27. Beatty PG, Ledbetter JA, Martin PJ, Price TH, Hansen JA: Definition of a

common leukocyte cell-surface antigen (Lp95-150) associated with diverse cell-mediated immune functions. J Immunol 1983; 131:2913-2918

28. Nuytinck HKS, Offermans XJMW, Kubat K, et al: Whole-body inflammation in trauma patients—An autopsy study. Arch Surg 1988; 123:1519-1524

29. Goris RJA, te Boekhorst TPA, Nuytinck JKS, Gimbrère JSF: Multiple-organ failure—Generalized autodestructive inflammation? Arch Surg 1985; 120:1109-1115

30. Vedder NB, Winn RK, Rice CL, Chi E, Arfors K, Harlan JM: A monoclonal antibody to the adherence promoting leukocyte glycoprotein CD18 reduces organ injury and improves survival from hemorrhagic shock and resuscitation in rabbits. J Clin Invest 1988; 81:939-944

31. Vedder NB, Fouty BW, Winn RK, Harlan JM, Rice CL: Role of neutrophils in generalized reperfusion injury associated with resuscitation from shock. Surgery 1989; 106:509-516

32. Mileski WJ, Winn RK, Vedder NB, Pohlman TH, Harlan JM, Rice CL: Inhibition of CD18-dependent neutrophil adherence reduces organ injury after hemorrhagic shock in primates. Surgery 1990; 108:206-212

33. Mileski WJ, Winn RK, Harlan JM, Rice CL: Transient inhibition of neutrophil adherence with the anti-CD18 monoclonal antibody (mAb 60.3) does not increase mortality in abdominal sepsis. Surgery 1991; 109:497-501

34. Sharar SR, Winn RK, Murry CE, Harlan JM, Rice CL: A CD18 monoclonal antibody increases the incidence and severity of subcutaneous abscess formation after high dose S. aureus injection in rabbits. Surgery 1991; 110:213-220

35. Hernandez LA, Grisham MB, Twohig B, Arfors KE, Harlan JM, Granger DN: Role of neutrophils in ischemia-reperfusion-induced microvascular injury. Am J Physiol 1987; 253:H699-703

36. Horgan MJ, Wright SD, Malik AB: Antibody against leukocyte integrin (CD18) prevents reperfusion-induced lung vascular injury. Am J Physiol 1990; 259:L315-L319

37. Carden DL, Smith JK, Korthuis RJ: Neutrophil-mediated microvascular dysfunction in postischemic canine skeletal muscle: Role of granulocyte adherence. Circ Res 1990; 66:1436-1444

38. Tuomanen EI, Saukkonen K, Sande S, Cioffe C, Wright SD: Reduction of inflammation, tissue damage, and mortality in bacterial meningitis in rabbit treated with monoclonal antibodies against adhesion-promoting receptors of leukocytes. J Exp Med 1989; 170:959-968

39. Simpson PJ, Todd RF III, Mickelson JK, et al: Sustained limitation of myocardial reperfusion injury by a monoclonal antibody that alters leukocyte function. Circulation 1990; 81:226-237

40. Hutchings P, Rosen H, O'Reilly L, Simpson E, Siamon G, Cook A: Transfer of diabetes in mice prevented by blockage of adhesion-promoting receptor on macrophages. Nature 1990; 346:636-642

41. Wegner CD, Gundel RH, Reilly P, Haynes N, Letts LG, Rothlein R: Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. Science 1990; 247:456-459

42. Cosimi AB, Conti D, Delmonico FL, et al: In vivo effects of monoclonal antibody to ICAM-1 (CD54) in nonhuman primates with renal allografts. J Immunol 1990; 144:4604-4612

CASE HISTORIES—ONCOLOGY

#49803

The x-ray portals are ruled with purple ink,
  those doors through which the pulses pass,
destroying the destroyer.

Indelible, the lines frame that place
  where diseased cells lurk
sparing neither age nor gender.

Some walk the hall unnoticed,
  marks hidden by their clothes,
while others bear the grid on head or face

like the tribal tattoos of a different race.

#38594

Meant to bring forth life
  her womb now bears her death;
that crimson velvet pocket
  in which to carry treasure,
holds instead a dreadful counterfeit.

#32457

Pink and hairless as an embryo the ten-year-old
  lies on the x-ray table and stares back
into the black barrel of the massive machine.

Back in the child's room the stuffed toys wait,
  On the wall beside the bed
the artwork done the day before.

In the picture a big black cannon
  is aimed directly at the brightly crayoned house
With the smiling family standing in the yard.

And yet the child has also drawn
  a delicate pink flower growing
inside the cannon's threatening mouth.

#84573

She lies alone and still in the darkening room
and wonders why she cannot feel
the invader rearrange
the structure of her brain.
A blessing, she supposes, and yet
she would almost rather feel some pain
to help her understand that this is real
and not some dream that she will soon
be lying alone and still within her tomb.

ANNE KAVANAUGH©
Crozet, Virginia