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REVIEW ARTICLE

Coagulation, Inflammation, and the Risk of Neonatal White Matter Damage

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Indicators of coagulation *activation* are sometimes increased in the blood of newborns and adults who have a systemic inflammatory response. These coagulation factors have the ability to exacerbate inflammation, which in turn can promote coagulation. Therapies directed solely at coagulation factors and therapies directed solely at inflammation factors have not proved effective in reducing mortality in adults with a systemic inflammatory response syndrome and multi-organ dysfunction (SIRS/MOD). On the other hand, the only therapy that has reduced mortality in SIRS/MOD is activated protein C, which has both anti-coagulation and anti-inflammatory effects. This and other observations support the view that *activated* coagulation factors enhance inflammation. Since newborns at risk of cerebral white matter damage and cerebral palsy are more likely than their peers to have a systemic inflammatory response, which is sometimes accompanied by elevated blood levels of coagulation factors, we suggest that activated coagulation factors contribute to the occurrence of cerebral white matter damage by exacerbating inflammatory phenomena, rather than by occluding cerebral blood vessels. **(*Pediatr Res* 55: 541–545, 2004)**

Abbreviations

CP, cerebral palsy
DIC, disseminated intravascular coagulation
RDS, respiratory distress syndrome
SIRS/MOD, systemic inflammatory response syndrome with multi-organ dysfunction
WMD, white matter damage

Preterm newborns with respiratory distress syndrome and term newborns who develop cerebral palsy tend to have elevated blood levels of coagulation factors. In this essay, we suggest that these coagulation factors, when activated, produce their effects not so much by promoting coagulation as by promoting inflammation, a view supported by studies of adults with a systemic inflammatory response syndrome with multi-organ dysfunction (SIRS/MOD). We also suggest that *activated* systemic coagulation factors in the preterm newborn contribute to cerebral white matter damage (WMD) and to its clinical sequelae, including cerebral palsy (CP).

NEWBORNS

Respiratory distress syndrome (RDS) in preterm newborns. Fibrin is a major part of hyaline membranes, which are viewed as locally produced clots in neonatal RDS (1, 2). Indeed, the severity of RDS has been linked to the systemic concentration of thrombin-antithrombin III complex (3). In addition, preterm babies with RDS are more likely than their peers to have systemic activation of inflammation (4, 5). We do not yet know if products of coagulation and inflammation co-occur in the blood of infants destined to develop bronchopulmonary dysplasia.

In newborn immature sheep with RDS, inflammation and clotting are activated shortly after birth (6). "Because activation of clotting and platelet activation are found later than activation of inflammation," Jaarsma and colleagues recently wrote, "we consider activation of clotting is not causative in RDS, but is activated secondary to activation of inflammation" (6).

We postulate that this scenario of inflammation promoting coagulation also applies to neonatal WMD. Moreover, we postulate that inflammation promotes coagulation, which in turn further promotes inflammation (Fig. 1).

CP in term newborns. Support for the systemic activation of both inflammation and coagulation in newborn brain damage comes from a study of term newborns who later developed CP (7). On postnatal day 2, these term babies had elevated levels of a factor V Leiden mutation product. This indicator of impaired anti-coagulation, however, was accompanied by prominent elevations of proteins with anti-coagulant properties (*e.g.* protein C, protein S, and antithrombin III). The elevation of these coagulation factors was accompanied by elevated blood levels of many pro-inflammatory cytokines and chemokines, supporting the view that coagulation activation and inflammation coexist, and may even influence one another.

Cerebral WMD in preterm newborns. Neurodevelopmental deficiencies are more common in preterm infants than in

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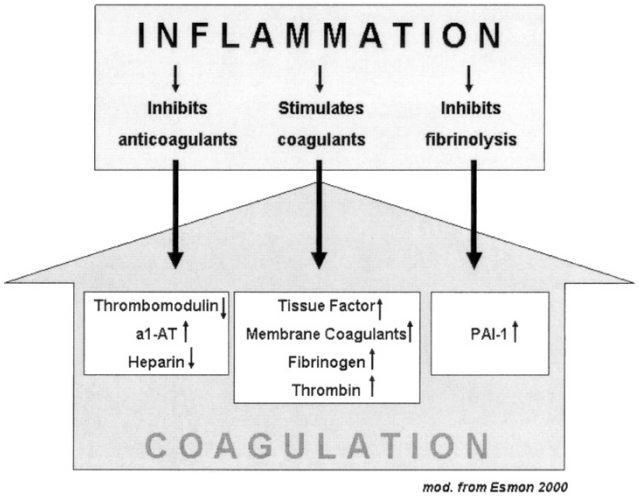

Figure 1. This figure emphasizes how an inflammatory stimulus promotes thrombin formation, impairs each of the three anti-coagulant pathways, and interferes with fibrinolysis. The resulting increased concentration of thrombin and decreased concentrations of anti-thrombin III, activated protein C, tissue factor pathway inhibitor, and plasminogen activator inhibitor 1 all contribute to enhancing inflammation.

infants born at term (8). Many of these can be predicted by the echolucent ultrasound images indicative of focal WMD (9). However, a considerable proportion of the brain dysfunction in these infants appears to be a consequence of a diffuse intracranial process (10). Since the available evidence does not support claims that echolucencies are ischemic lesions (11), our discussion of activated coagulation factors and brain damage in no way implies that the damage is a consequence of intravascular coagulation leading to ischemia.

Chorioamnionitis predicts ultrasound-defined WMD and CP (12). The more this inflammatory response involves the fetus, the greater the risk of brain damage (13). Infection remote from the brain appears to increase the systemic availability of inflammatory products, which gain access to the fetal/newborn brain where they do their damage (14, 15). Indeed, newborns with elevated circulating levels of inflammatory cytokines are at increased risk of WMD and CP (16). The strongest support for a fetal contribution to this systemic inflammatory response is the presence of inflammatory products in umbilical cord blood (17).

The coexistence of inflammatory and thrombotic lesions in the preterm placenta is associated with heightened risk of neurologic impairment (18). These findings, along with the co-occurrence of markers of inflammation and coagulation in term newborns who develop CP (7), raise the possibility that increased circulating levels of activated coagulation factors enhance the influence of inflammation factors. In one highly selected sample, however, preterm newborns who developed CP had mean and median values of anti-thrombin that were similar to those of controls (19).

Preterm newborns with the Val34Leu polymorphism of the factor XIII gene appear to be at *reduced* risk of WMD (20). Adults with this polymorphism produce a less stable fibrin clot than people without (21), are at increased risk of intracerebral hemorrhage (22) and are at *reduced* risk of brain and myocardial infarction and venous thrombosis (23–25). These observations suggest that the reduced risk of WMD in preterm newborns is due to a reduced risk of fibrin clot obstruction of cerebral blood flow.

However, what the authors of this report (20) attribute to ischemia, might just as readily be due to inflammation. Fibrin has inflammatory properties (26). Circumstantial evidence for this comes from diverse sources. Depression of plasminogen activator-mediated fibrinolysis not only increases fibrin deposition in alveoli, but also contributes to inflammatory cell recruitment and migration (27). Fibrinolytic strategies to block pulmonary and pleural fibrin deposition and inflammation appear promising (28).

An imbalance between fibrin deposition and fibrin dissolution contributes to inflammation-induced peritoneal adhesions (29). In addition, mice deficient in tPA are more susceptible to inflammation-induced adhesion formation than wild-type mice (30).

Additional evidence for the inflammatory properties of fibrin comes from studies of bacteria and humans. The conversion of fibrinogen to fibrin at the surface of bacteria generates proinflammatory fibrinopeptides (31). People who have genetic polymorphisms that lead to excess expression of PAI-1 also have increased levels of TNF-alpha, and IL-1 (32). Some view the relationship between fibrin and inflammation so convincing that they advocate plasminogen activator inhibitors as therapy for sepsis (33).

Individuals with the factor XIII Val34Leu polymorphism have less fibrin than their peers (21) and should, therefore, be less able to mount a vigorous inflammatory response than individuals without this polymorphism. Since some WMD or CP appears to follow a vigorous fetal or neonatal inflammatory response (13), newborns with a factor XIII Val34Leu polymorphism should be at reduced risk of WMD and CP. This reasoning does not diminish the contribution of coagulation products to the occurrence of WMD. It just changes the focus from ischemia to inflammation.

Adult studies and animal models. More research appears to be devoted to the study of systemic inflammation in the adult than in the newborn. Perhaps we can learn from the progress being made in studies of sepsis and SIRS/MOD (34).

Inflammation promotes coagulation. Sepsis and SIRS/MOD are accompanied by thrombin generation, impaired anticoagulation, and impaired fibrinolysis (35). Each can be initiated by endotoxemia (36) and pro-inflammatory cytokines (37).

Coagulation promotes inflammation. Coagulation products with pro-inflammatory effects include factor Xa (38), tissue factor (39), fibrinogen/fibrin (28), plasmin (40), and thrombin (41). Thrombin signaling is probably achieved by activating the PAR-1-type thrombin receptor (42). This in turn stimulates endothelial cell activation, resulting in the availability of adhesion molecules (43), which facilitate the transendothelial migration of leukocytes into the surrounding parenchyma (44). Endothelial cell activation also promotes the synthesis of proinflammatory cytokines (45).

Disseminated intravascular coagulation. "Many investigators currently believe that it is not DIC, and particularly not

fibrin formation itself that is harmful, but rather it is the generation of serine proteases and their potential interactions with pro-inflammatory mediators that contributes to organ failure and death" (46). Thus, markers of coagulation dysfunction in the blood (and perhaps the lung and brain) might provide more information about inflammation than they do about the obstruction of microvessels.

Inflammation and coagulation amplify each other. Whether coagulation is a cascade or a sequence of overlapping stages (47), inflammation and coagulation amplify each other (43). A "vicious cycle" does not automatically follow because some proteins with anti-coagulant *and* anti-inflammatory properties are released in response to products of coagulation (43).

Activated protein C. Impairments of the protein C system are a hallmark of adult sepsis (48). Activated protein C has anti-thrombotic, pro-fibrinolytic, and anti-inflammatory properties (49).

Activated protein C modulates coagulation by decreasing synthesis and expression of tissue factor (50). By forming a complex with protein S, activated protein C inactivates factors Va and VIIIa, thereby limiting production of thrombin (51), and limiting activation of factor X (52).

Activated protein C increases fibrinolysis by decreasing plasminogen activator inhibitor 1 and thereby preventing inhibition of tPA (53). Less directly, activated protein C promotes fibrinolysis by inhibiting thrombin formation (54), which in turn, limits the activation of thrombin activatable fibrinolysis inhibitor (55).

Reduced inflammation is achieved by limiting the production of thrombin (51, 54), inhibiting neutrophil binding to selectins (56), and limiting the production of monocyte chemoattractant protein-1 (57). Activated protein C also inhibits TNF-alpha production by monocytes and endothelial cells (58, 59), apparently by interfering with nuclear factor-κB nuclear translocation (60, 61) and the binding of STAT6 oligonucleotides to nuclear proteins (62). In addition, during translocation from the plasma membrane, the endothelial cell protein C receptor can carry activated protein C to the nucleus, where activated protein C is presumed to modulate inflammatory mediator responses in the endothelium (35).

Activated protein C in models of SIRS. In a rat model of lipopolysaccharide-induced lung microvascular injury, a potent inhibitor of thrombin generation blocks neither lung injury nor the increase in plasma concentration of tumor necrosis factor-alpha (59). On the other hand, both are blocked by activated protein C.

In a baboon model of DIC induced with live *Escherichia coli*, an inhibitor of thrombin generation prevents DIC, but not shock and multiple organ failure (63). In contrast, activated protein C prevented DIC, shock and multiple organ failure (63).

Clinical trials of activated protein C to reduce mortality in SIRS/MOD. Most attempts to reduce the very high mortality rate in people with SIRS/MOD have been disappointing. Some therapies were intended to reduce the inflammatory response, others to reduce DIC (*e.g.*, by inhibiting thrombin generation) (64). DIC was reduced in some studies, but mortality was not. On the other hand, activated protein C, which suppresses thrombin generation and has indirect and direct anti-inflammatory properties, has reduced mortality in SIRS/MOD (48).

In the largest clinical trial that documented the effectiveness of activated protein C to prevent death in SIRS/MOD, drug recipients had lower plasma levels of IL-6 and thrombin-related biomarkers than placebo recipients (48). Apparently, both anti-inflammatory and anti-coagulation properties contribute to the effectiveness of activated protein C.

Inferences for newborns. What we discussed above might be relevant to neonatal WMD. Inferences can be drawn in three areas: coagulation activation, endothelial activation, and the therapeutic benefits of endogenous activated protein C.

Both endotoxin and pro-inflammatory cytokines promote thrombin generation, impair anticoagulation, and diminish fibrinolysis (36, 37). Both endotoxin and pro-inflammatory cytokines have also been implicated in the pathogenesis of WMD in newborn animals (65) and humans (16). Perhaps thrombin generation, impaired anticoagulation, and diminished fibrinolysis contribute to WMD.

Funisitis (umbilical cord vessel inflammation) can be viewed as a histologic expression of endothelial activation. Infants with funisitis appear to be at increased risk of WMD, CP, and other neurodevelopmental dysfunctions (18, 66–68). In addition, products of inflammation synthesized by endothelial cells have been implicated in WMD pathogenesis (16). Since thrombin's activation of endothelial cells results in multiple inflammatory phenomena (35), thrombin activation of umbilical cord endothelial cells might contribute to the occurrence of WMD in preterm newborns.

Proinflammatory cytokines activate synthesis of inducible nitric oxide synthase, which is required for the production of nitric oxide and its breakdown products, free nitrogen and oxygen radicals (69, 70). Some of the brain damage initiated by inflammatory cytokines requires the presence of inducible nitric oxide synthase iNOS (71). Consequently, evidence that newborn white matter damage is due to fetal inflammatory phenomena (72) is entirely compatible with evidence that free oxygen radicals contribute to the demise of oligodendrocyte precursors *in vitro* (73), brain lesions in rodents (34), and lipid peroxidation in premyelinating oligodendrocytes in humans (74). Coagulation proteins can contribute to brain damage *via* the production of free radicals secondary to inflammatory phenomena, as well as by more direct means (75).

The success of activated protein C therapy in adults with SIRS/MOD suggests that therapies intended to reduce the organ damage accompanying fetal and neonatal inflammatory responses should have both anti-inflammatory and anti-coagulation properties. Activated protein C also has neuroprotective effects independent of its systemic anti-coagulant and anti-inflammatory functions (76). Nevertheless, in light of bleeding and other complications (77), we urge caution in considering activated protein C for preterm newborns with evidence of a systemic inflammatory response. A prudent course would be to delay consideration of clinical trials of activated protein C until laboratory models show that activated protein C is effective in reducing the risk of white matter damage. Although not needed to demonstrate effectiveness,

additional epidemiologic studies would support the decision to test activated protein C in humans if they found that thrombin-related biomarkers are elevated in the blood of newborns who develop white matter damage and/or cerebral palsy.

Shortly after birth at term, protein C levels in the blood are almost 40% of those in adults (78). They are even lower in those born before term (79). In light of our suggestion that the fetal and neonatal inflammatory responses activate the clotting system, such low levels of protein C might place the newborn at especially high risk of the inflammatory consequences of clotting system activation. Because protein C levels rise following vitamin K administration (80), the recommendation that all babies receive vitamin K prophylaxis to prevent hemorrhagic disease of the newborn (81) might have the added benefit of reducing the heightened inflammatory response seen in preterm newborns.

CONCLUSION

Our hypothesis that activated coagulation products contribute to the occurrence of neonatal lung disease and WMD should be viewed as tenuous. We doubt that organ damage in preterm newborns who have elevated blood levels of coagulation factors can be attributed solely to vessel occlusion. Rather, we infer from the current literature that in preterm newborns with a systemic inflammatory response, activation of the coagulation system contributes to organ damage by promoting inflammation.

REFERENCES

1. Singhal KK, Parton LA 1996 Plasminogen activator activity in preterm infants with respiratory distress syndrome: relationship to the development of bronchopulmonary dysplasia. Pediatr Res 39:229–235
2. Chan AK, Berry L, Mitchell L, Baranowski B, O'Brodovich H, Andrew M 1998 Effect of a novel covalent antithrombin-heparin complex on thrombin generation on fetal distal lung epithelium. Am J Physiol 274:L914–921
3. Schmidt BK 1994 Antithrombin III deficiency in neonatal respiratory distress syndrome. Blood Coagul Fibrinolysis 5 Suppl 1:S13–17; discussion S59–64
4. Brus F, van Oeveren W, Okken A, Oetomo SB 1994 Activation of the plasma clotting, fibrinolytic, and kinin-kallikrein system in preterm infants with severe idiopathic respiratory distress syndrome. Pediatr Res 36:647–653
5. Brus F, Van Oeveren W, Okken A, Oetomo SB 1997 Disease severity is correlated with plasma clotting and fibrinolytic and kinin-kallikrein activity in neonatal respiratory distress syndrome. Pediatr Res 41:120–127
6. Jaarsma AS, Braaksma MA, Geven WB, Van Oeveren W, Oetomo SB 2001 Early activation of inflammation and clotting in the preterm lamb with neonatal RDS: comparison of conventional ventilation and high frequency oscillatory ventilation. Pediatr Res 50:650–657
7. Nelson K, Dambrosia J, Grether JK, Phillips TM 1998 Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 44:665–675
8. McGrath MM, Sullivan MC, Lester BM, Oh W 2000 Longitudinal neurologic follow-up in neonatal intensive care unit survivors with various neonatal morbidities. Pediatrics 106:1397–1405
9. Paneth N, Rudelli R, Kazam E, Monte W 1994 Brain Damage in the Preterm Newborn. Mac Keith Press, London
10. Counsell SJ, Rutherford MA, Cowan FM, Edwards AD 2003 Magnetic resonance imaging of preterm brain injury. Arch Dis Child Fetal Neonatal Ed 88:F269–274
11. Kuban K 1998 White-matter disease of prematurity, periventricular leukomalacia, and ischemic lesions. Dev Med Child Neurol 40:571–573
12. Wu YW 2002 Systematic review of chorioamnionitis and cerebral palsy. Ment Retard Dev Disabil Res Rev 8:25–29
13. Yoon BH, Park CW, Chaiworapongsa T 2003 Intrauterine infection and the development of cerebral palsy. BJOG 110 Suppl 20:124–127
14. Dammann O, Leviton A 1997 Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 42:1–8
15. Dammann O, Leviton A 1998 Infection remote from the brain, neonatal white matter damage, and cerebral palsy in the preterm infant. Semin Pediatr Neurol 5:190–201
16. Leviton A, Dammann O, O'Shea TM, Paneth N 2002 Adult stroke and perinatal brain damage: like grandparent, like grandchild? Neuropediatrics 33:281–287
17. Pacora P, Chaiworapongsa T, Maymon E, Kim YM, Gomez R, Yoon BH, Ghezzi F, Berry SM, Qureshi F, Jacques SM, Kim JC, Kadar N, Romero R 2002 Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflammatory response syndrome. J Matern Fetal Neonatal Med 11:18–25
18. Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M 2000 The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. Pediatr Res 47:721–726
19. Nelson KB, Grether JK, Dambrosia JM, Walsh E, Kohler S, Satyanarayana G, Nelson PG, Dickens BF, Phillips TM 2003 Neonatal cytokines and cerebral palsy in very preterm infants. Pediatr Res 111:674–679
20. Gopel W, Kattner E, Seidenberg J, Kohlmann T, Segerer H, Moller J, Group GFiNS 2002 The effect of the Val34Leu polymorphism in the factor XIII gene in infants with a birth weight below 1500 g. J Pediatr 140:688–692
21. Ariens R, Philippou H, Nagaswami C, Weisel J, Lane D, Grant P 2000 The factor XIII V34L polymorphism accelerates thrombin activation of factor XIII and affects cross-linked fibrin structure Blood 96:988–995
22. Catto A, Kohler H, Bannan S, Stickland M, Carter A, Grant P 1998 Factor XIII Val34Leu, a novel association with primary intracerebral hemorrhage. Stroke 29:813–816
23. Catto A, Kohler H, Coore J, Mansfield M, Stickland M 1999 Association of a common polymorphism in the factor XIII gene with venous thrombosis. Blood 93:906–908
24. Elbaz A, Poirier O, Canaple S, Chedru F, Cambien F, Amarenco P 2000 The association between the Val34Leu polymorphism in the factor XIII gene and brain infarction. Blood 95:986–991
25. Kohler H, Stickland M, Ossei-Gerning N, Carter A, Mikkola H, Grant P 1998 Association of a common polymorphism in the factor XIII gene with myocardial infarction. Thromb Haemost 79:8–13
26. Degen J 1999 Hemostatic factors and inflammatory disease. Thromb Haemost 82:858–864
27. Levi M, Schultz MJ, Rijneveld AW, van der Poll T 2003 Bronchoalveolar coagulation and fibrinolysis in endotoxemia and pneumonia. Crit Care Med 31:S238–242
28. Idell S 2003 Coagulation, fibrinolysis, and fibrin deposition in acute lung injury Crit Care Med 31:S213–220
29. Holmdahl L 1997 The role of fibrinolysis in adhesion formation. Eur J Surg Suppl 577:24–31
30. Sulaiman H, Dawson L, Laurent GJ, Bellingan GJ, Herrick SE 2002 Role of plasminogen activators in peritoneal adhesion formation. Biochem Soc Trans 30:126–131
31. Persson K, Russell W, Morgelin M, Herwald H 2003 The conversion of fibrinogen to fibrin at the surface of curliated Escherichia coli bacteria leads to the generation of proinflammatory fibrinopeptides. J Biol Chem 278:31884–31890
32. Russell JA 2003 Genetics of coagulation factors in acute lung injury. Crit Care Med 31:S243–247
33. Pechlaner C 2002 Plasminogen activators in inflammation and sepsis. Acta Med Austriaca 29:80–88
34. Plaisant F, Clippe A, Vander Stricht D, Knoops B, Gressens P 2003 Recombinant peroxiredoxin 5 protects against excitotoxic brain lesions in newborn mice Free Radic Biol Med 34:862–872
35. Esmon CT 2003 Inflammation and thrombosis. J Thromb Haemost 1:1343–1348
36. Franco R, de Jonge E, Dekkers P, Timmerman J, Spek C, van Deventer S, van Deursen P, van Kerkhoff L, van Gemen B, ten Cate H, van der Poll T, Reitsma P 2000 The *in vivo* kinetics of tissue factor messenger RNA expression during human endotoxemia Relationship with activation of coagulation. Blood 96:554–559
37. ten Cate JW, van der Poll T, Levi M, ten Cate H, van Deventer SJ 1997 Cytokines: triggers of clinical thrombotic disease. Thromb Haemost 78(1):415–419
38. Altieri D 1994 Molecular cloning of effector cell protease receptor-1, a novel cell surface receptor for the protease factor Xa. J Biol Chem 269:3139–3142
39. Cunningham M, Romas P, Hutchinson P, Holdsworth S, Tipping P 1999 Tissue factor and factor VIIa receptor/ligand interactions induce proinflammatory effects in macrophages. Blood 94:3413–3420
40. Rhee JS, Santoso S, Herrmann M, Bierhaus A, Kanse SM, May AE, Nawroth PP, Colman RW, Preissner KT, Chavakis T 2003 New aspects of integrin-mediated leukocyte adhesion in inflammation: regulation by haemostatic factors and bacterial products. Curr Mol Med 3:387–392
41. Coughlin SR 2000 Thrombin signalling and protease-activated receptors. Nature 407:258–264
42. Cirino G, Bucci M, Cicala C, Napoli C 2000 Inflammation-coagulation network: are serine protease receptors the knot? Trends Pharmacol Sci 21:170–172
43. Levi M, ten Cate H, van der Poll T 2002 Endothelium Interface between coagulation and inflammation. Crit Care Med 30:S220–S224
44. Harlan JM, Winn RK 2002 Leukocyte-endothelial interactions: clinical trials of anti-adhesion therapy. Crit Care Med 30:S214–219
45. Krishnaswamy G, Kelley J, Yerra L, Smith JK, Chi DS 1999 Human endothelium as a source of multifunctional cytokines: Molecular regulation and possible role in human disease. J Interferon Cytokine Res 19:91–104
46. ten Cate H, Schoenmakers SH, Franco R, Timmerman JJ, Groot AP, Spek CA, Reitsma PH 2001 Microvascular coagulopathy and disseminated intravascular coagulation. Crit Care Med 29:S95–98
47. Hoffman M, Monroe DM, 3rd 2001 A cell-based model of hemostasis. Thromb Haemost 85:958–965
48. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ, Jr., Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group 2001 Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709

49. Joyce D, Grinnell B 2002 Recombinant human activated protein C attenuates the inflammatory response in endothelium and monocytes by modulating nuclear factor-κB. Crit Care Med 30:S288–S293
50. Shu F, Kobayashi H, Fukudome K, Tsuneyoshi N, Kimoto M, Terao T 2000 Activated protein C suppresses tissue factor expression on U937 cells in the endothelial protein C receptor-dependent manner FEBS Lett 477:208–212
51. Nicolaes GA, Dahlback B 2002 Factor V, and thrombotic disease: description of a janus-faced protein. Arterioscler Thromb Vasc Biol 22:530–538
52. Dahlback B, Villoutreix BO 2003 Molecular recognition in the protein C anticoagulant pathway. J Thromb Haemost 1:1525–1534
53. Sakata Y, Loskutoff DJ, Gladson CL, Hekman CM, Griffin JH 1986 Mechanism of protein C-dependent clot lysis: role of plasminogen activator inhibitor. Blood 68:1218–1223
54. Esmon CT 2001 The normal role of Activated Protein C in maintaining homeostasis and its relevance to critical illness. Crit Care 5 Suppl 2:S7–S12
55. Mosnier LO, Elisen MG, Bouma BN, Meijers JC 2001 Protein C inhibitor regulates the thrombin-thrombomodulin complex in the up- and down regulation of TAFI activation Thromb Haemost 86:1057–1064
56. Grinnell BW, Hermann RB, Yan SB 1994 Human protein C inhibits selectin-mediated cell adhesion: role of unique fucosylated oligosaccharide. Glycobiol 4:221–225
57. Brueckmann M, Marx A, Weiler HM, Liebe V, Lang S, Kaden JJ, Zieger W, Borggrefe M, Huhle G, Konstantin Haase K 2003 Stabilization of monocyte chemoattractant protein-1-mRNA by activated protein C. Thromb Haemost 89:149–160
58. Hancock WW, Tsuchida A, Hau H, Thomson NM, Salem HH 1992 The anticoagulants protein C and protein S display potent antiinflammatory and immunosuppressive effects relevant to transplant biology and therapy. Transplant Proc 24:2302–2303
59. Murakami K, Okajima K, Uchiba M, Johno M, Nakagaki T, Okabe H, Takatsuki K 1997 Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. Am J Physiol 272:L197–202
60. White B, Schmidt M, Murphy C, Livingstone W, O'Toole D, Lawler M, O'Neill L, Kelleher D, Schwarz HP, Smith OP 2000 Activated protein C inhibits lipopolysaccharide-induced nuclear translocation of nuclear factor kappaB (NF-kappaB) and tumour necrosis factor alpha (TNF-alpha) production in the THP-1 monocytic cell line. Br J Haematol 110:130–134
61. Yuksel M, Okajima K, Uchiba M, Horiuchi S, Okabe H 2002 Activated protein C inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production by inhibiting activation of both nuclear factor-kappa B, and activator protein-1 in human monocytes. Thromb Haemost 88:267–273
62. Yuda H, Adachi Y, Taguchi O, Gabazza EC, Hataji O, Fujimoto H, Tamaki S, Nishikubo K, Fukudome K, D'Alessandro-Gabazza CN, Maruyama J, Izumizaki M, Iwase M, Homma I, Inoue R, Kamada H, Hayashi T, Kasper M, Barnes PJ, Suzuki K 2003 Activated protein C inhibits bronchial hyperresponsiveness and Th2 cytokine expression in the mouse. Blood Nov 6 [Epub ahead of print]
63. Esmon CT, Taylor FB, Snow T 1991 Inflammation and coagulation: linked processes potentially regulated through a common pathway mediated by protein C. Thromb Haemost 60:160–165
64. Vincent JL, Jacobs F 2003 Infection in critically ill patients: clinical impact and management. Curr Opin Infect Dis 16:309–313
65. Hagberg H, Peebles D, Mallard C 2002 Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. Ment Retard Dev Disabil Res Rev 8:30–38
66. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, Pagano M, for the Developmental Epidemiology Network Investigators 1999 Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Pediatr Res 46:566–575
67. Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH, Han TR 2000 Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 182:675–681
68. Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M 1998 Placental lesions associated with neurologic impairment and cerebral palsy in very low-birthweight infants. Arch Pathol Lab Med 122:1091–1098
69. Hibbs JB Jr, Westenfelder C, Taintor R, Vavrin Z, Kablitz C, Baranowski RL, Ward JH, Menlove RL, McMurry MP, Kushner JP, Samlowski WE 1992 Evidence for cytokine-inducible nitric oxide synthesis from L-arginine in patients receiving interleukin-2 therapy. J Clin Invest 89:867–877
70. Kilbourn RG, Griffith OW 1992 Overproduction of nitric oxide in cytokine-mediated and septic shock. J Natl Cancer Inst 84:827–831
71. Stoll G, Jander S, Schroeter M 2000 Cytokines in CNS disorders: neurotoxicity versus neuroprotection J Neural Transm Suppl 59:81–89
72. Dammann O, Leviton A 2000 Role of the fetus in perinatal infection and neonatal brain damage. Curr Opin Pediatr 12:99–104
73. Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ 1998 Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J Neurosci 18:6241–6253
74. Haynes RL, Folkerth RD, Keefe RJ, Sung I, Swzeda LI, Rosenberg PA, Volpe JJ, Kinney HC 2003 Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. J Neuropathol Exp Neurol 62:441–450
75. Holland JA, Meyer JW, Chang MM, O'Donnell RW, Johnson DK, Ziegler LM 1998 Thrombin stimulated reactive oxygen species production in cultured human endothelial cells. Endothelium 6:113–121
76. Cheng T, Liu D, Griffin JH, Fernandez JA, Castellino F, Rosen ED, Fukudome K, Zlokovic BV 2003 Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective. Nat Med 9:338–342
77. Freeman BD, Zehnbauer BA, Buchman TG 2003 A meta-analysis of controlled trials of anticoagulant therapies in patients with sepsis. Shock 20:5–9
78. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P 1987 Development of the human coagulation system in the full-term infant. Blood 70:165–172
79. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Castle V, Powers P 1988 Development of the human coagulation system in the healthy premature infant. Blood 72:1651–1657
80. McNinch AW, Upton C, Samuels M, Shearer MJ, McCarthy P, Tripp JH, R L'E Orme R 1985 Plasma concentrations after oral or intramuscular vitamin K1 in neonates. Arch Dis Child 60:814–818
81. 2003 Controversies concerning vitamin K and the newborn. American Academy of Pediatrics Committee on Fetus and Newborn Pediatrics 112:191–192