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Pathogenesis of Disseminated Intravascular Coagulation in Sepsis

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Objective.—To review new insights in the pathogenetic mechanisms involved in the development of disseminated intravascular coagulation (DIC) in septic patients, in order to develop new directions for therapeutic intervention.

Data Sources.—Articles and published peer-reviewed abstracts on the mechanism of the initiation of DIC in sepsis.

Study Selection.—Studies selected for detailed review were those reporting specifics about the mechanism of activation of coagulation and fibrinolysis in experimental human and animal models of sepsis. Data extraction guidelines for assessing data quality included validity of the model, quality of the laboratory assessment of activation of coagulation and fibrinolysis, and methodological considerations, such as the presence of control experiments and statistical analysis.

Data Synthesis.—After the presence of endotoxin in the circulation, significant coagulation activation can be detected. This activation is preceded by an increase in the serum levels of various cytokines, such as tumor necrosis factor and interleukins. Inhibition of the increase in tumor necrosis factor results in inhibition of coagulation activation. Measurement of molecular markers for the activation of coagulation proteins at various levels indicates that the activation of coagulation is mediated by the tissue factor–dependent pathway, which is further confirmed by experiments in which the inhibition of the tissue factor–dependent pathway resulted in complete inhibition of coagulation activation. The activation of coagulation seems to be amplified by impaired function of the protein C–protein S inhibitory pathway. An imbalance between coagulation and fibrinolysis, ultimately leading to plasminogen activator inhibitor type 1–mediated inhibition of fibrinolysis, may further promote the procoagulant state.

Conclusion.—The increased knowledge of the various pathogenetic mechanisms of coagulation activation and fibrinolysis in sepsis may have therapeutic implications; however, their efficacy needs to be assessed in appropriate clinical trials.

(*JAMA.* 1993;270:975-979)

IN SEPTIC patients, disseminated intravascular coagulation (DIC) occurs frequently. Disseminated intravascular coagulation may complicate the already complex clinical situation and contribute to the high mortality. Coagulation activation in sepsis may become apparent in several ways.[1,2] First, the systemic activation of blood coagulation results in generation and deposition of fibrin, leading to the formation of microvascular thrombi in various organs,[2,3] which may be involved in the pathogenesis of the multiple organ failure. Second, depletion of coagulation proteins, due to the extensive and ongoing activation of the coagulation system (and possibly also by impaired liver synthesis and by activated protease-mediated destruction of coagulation factors), may induce severe bleeding complications. The primary treatment of DIC in septic patients should be directed at the underlying disease (eg, by antibiotics or surgical intervention), but clinically important thrombus formation and the simultaneous occurrence of bleeding may require additional supportive measures. However, an effective and safe therapy that has been evaluated in a controlled clinical trial is not available.

To develop a rational treatment for DIC in septic patients, the pathogenetic mechanisms by which the activation of coagulation in the sepsis syndrome occurs have to be understood. Recent observations in septic patients as well as in models of experimental septicemia that use sensitive and specific immunoassays have partly elucidated these mechanisms. In this article, we review recent studies on the routes of coagulation activation and fibrinolysis that are activated by endotoxin and cytokines.

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EXPERIMENTAL SEPSIS MODELS

The studies selected for this review are clinical studies in septic patients as well as experimental studies in human volunteers and primates. In vitro studies were excluded from this review because it is difficult to translate in vitro results to the in vivo situation. Studies in smaller animals, such as rats and rabbits, have been excluded because these models are difficult to compare with the human situation. All studies in humans or in primates that were selected for this review were controlled studies in which sensitive and specific markers for coagulation activation at various levels were assessed, such as measurements of peptides liberated from coagulation factor zymogens during their activation or detection of complexes between activated coagulation factors and their natural inhibitors.

ENDOTOXINS AND CYTOKINES

Endotoxins, lipopolysaccharide constituents of the outer membrane of gram-negative microorganisms, play a pivotal role in the development of the sepsis syndrome.[4] In septic patients, levels of circulating endotoxin (normally not present in the blood) are detectable and are prognostic markers for the clinical outcome of the septic syndrome.[5,6] Laboratory and clinical evidence indicates that the toxic effects of endotoxin are mediated by cytokines, of which tumor necrosis factor–α (TNF-α) appears to play a particularly important mediatory role in the development of septicemia.[7] However, with the exception of fulminant meningococcal sep-

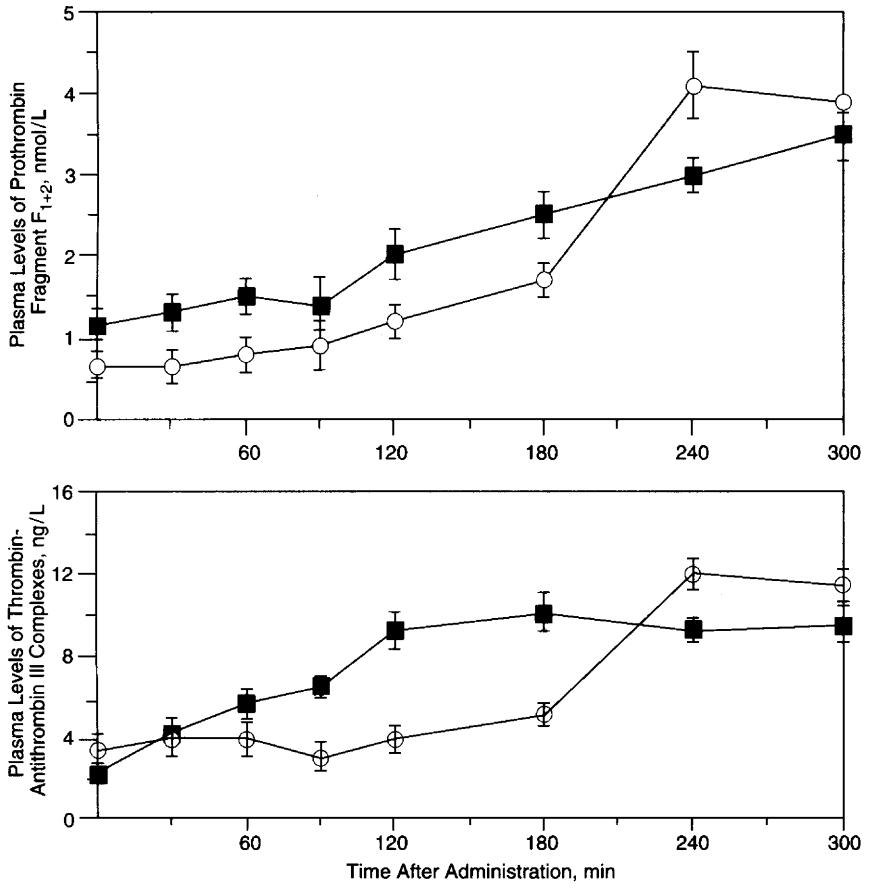

Fig 1.—Generation of thrombin as reflected by plasma levels of prothrombin activation fragment F_{1+2} (upper panel) and plasma levels of thrombin–antithrombin III complex (lower panel) after the intravenous injection of endotoxin or recombinant tumor necrosis factor–α (TNF-α) in healthy volunteers. Six healthy volunteers were infused with US standard endotoxin (EC-5) at a bolus dosage of 2 ng/kg (circles)[9] and another six healthy volunteers received a bolus dose of recombinant TNF-α at a dosage of 50 μg/kg (squares).[12] Mean values ±SD are given. The rise in plasma levels of F_{1+2} and thrombin–antithrombin III complexes is statistically significant at 240 and 300 minutes after the administration of endotoxin (compared with baseline levels) and is statistically significant at 280 minutes and further on after the administration of TNF-α (compared with baseline levels). The increase in prothrombin activation fragment F_{1+2} after the injection of endotoxin is approximately 60 minutes delayed compared with the increase after the injection of TNF-α, suggesting an intermediary role of TNF-α in endotoxin-induced coagulation activation.

sis, it has been difficult to demonstrate a causal relationship between the appearance of endotoxin and cytokines in the circulation and activation of the coagulation and fibrinolytic systems. Administration of low doses of endotoxin to healthy volunteers resulted in the transient occurrence of a sepsis-like syndrome, and enhanced serum levels of several cytokines were observed.[8,9] Subsequently, serum levels of TNF-α became first detectable, peaking at 90 minutes after the infusion of endotoxin and thereafter gradually declining.[9] This peak was followed by an increase in circulating levels of interleukin 6 and interleukin 8, peaking at 120 minutes after the infusion of endotoxin,[9,10] suggesting a possible role of these proteins in the development of the septic syndrome as well. The increase in cytokines was followed by a marked increase in circulating markers for the generation of thrombin (prothrombin fragment F_{1+2} and thrombin-antithrombin III complexes), as illustrated in Fig 1, and in markers for fibrinogen-to-fibrin conversion (fibrinopeptide A).[9] This observation indicated that indeed the presence of low circulating levels of endotoxins can induce coagulation activation and suggests that this effect is mediated by cytokines. Interestingly, after the injection of low-dose recombinant TNF-α in cancer patients and in healthy volunteers, a similar activation of the coagulation system was observed, thereby indicating an important mediatory role of TNF-α in the pathogenesis of septicemia.[11,12] Recent studies in which chimpanzees were injected with endotoxin in combination with pentoxifylline (which is able to block TNF-α expression)[13] showed that inhibition of endotoxin-induced TNF-α release resulted in inhibition of coagulation activation.[14] These observations confirmed the central role of TNF-α as a mediator of endotoxin-induced coagulation activation. The significance of other cytokines such as interleukin 1, interleukin 6, and interleukin 8 for the activation of coagulation in sepsis has not been completely elucidated. These cytokines, particularly interleukin 1, have significant effects on blood coagulation in vitro,[15,16] and a mediatory role of these proteins in endotoxin-induced activation of coagulation is certainly not excluded.

COAGULATION ACTIVATION

The generation of thrombin is a result of activation of either the intrinsic (or contact-activation dependent) pathway or the extrinsic (tissue-factor dependent) pathway, shown in Fig 2. Initial in vitro studies showed that very high concentrations of endotoxin could directly activate factor XII (an important factor in the contact activation system),[17] and clinical studies showed very low levels of factor XII in septic patients,[18,19] thereby suggesting a pivotal role for the intrinsic route in the activation of the coagulation system. However, recent studies of experimental endotoxemia or cytokinemia, using highly sensitive and specific assays for activation of the various coagulation factors, indicate that the initial activation of coagulation in sepsis is primarily dependent on activation of the extrinsic (tissue-factor dependent) pathway.[9,12] First, after injection of endotoxin in healthy volunteers or chimpanzees or following the infusion of TNF-α in healthy volunteers or cancer patients, substantial factor X–mediated generation of thrombin could be observed, whereas plasma levels of markers for intrinsic pathway activation (ie, factor XIIa-C1 inhibitor complexes, kallikrein-C1 inhibitor complexes, and factor IX activation peptide) remained within the normal range.[9,11,12,14] Second, in vitro studies have shown that TNF-α induces the expression of tissue factor on monocytes.[20] Tissue factor binds and activates factor VII, thereby forming a tissue factor–factor VIIa complex, which is able to convert factor X into factor Xa. Clinical studies in children with meningococcal sepsis showed increased tissue factor expression on circulating monocytes.[21] In addition, substantial amounts of tissue factor are expressed at subendothelial sites, and these stores may be exposed to the circulating blood in case of increased vascular permeability in the presence of endotoxin and/or cytokines.[22,23] Final proof for the primary role of the extrinsic pathway was derived from studies of experimental bacteremia or endotoxemia in baboons or chimpanzees in which the extrinsic system was blocked by the simultaneous infusion of monoclonal antibodies, either directed against tissue factor or directed

against factor VIIa.[14,24,25] In these studies, the endotoxin-induced thrombin generation and fibrinogen-to-fibrin conversion was completely inhibited by blocking the extrinsic pathway. Endotoxin-induced activation of blood coagulation seems to be mediated in part by TNF-α and at least initially to depend on activation of the extrinsic pathway of blood coagulation.

THE PROTEIN C–PROTEIN S SYSTEM

The coagulation system has various inhibitory systems such as the antithrombin–heparan sulfate system and the protein C–protein S system. For the development of DIC in septicemia, the protein C–protein S system (Fig 3) appears to be important. Activated protein C is an important inhibitor of coagulation factors V and VIII. The activation of protein C is induced by a complex that is formed between thrombin and the endothelial cell surface protein, thrombomodulin. The anticoagulant capacity of protein C is greatly enhanced by the noncomplexed part of its natural cofactor protein S, most of which is bound to a complement regulatory protein, C4b binding protein (C4bBP). Tumor necrosis factor–α downregulates thrombomodulin expression on endothelial cells, resulting in a decreased protein C activity, thus further contributing to a procoagulant state.[26,27] The importance of the protein C–protein S system for the development of DIC in septic patients was further emphasized by experiments in *Escherichia coli*–induced septicemia in baboons.[28] In these experiments, interference with activation of protein C by monoclonal antibodies resulted in the occurrence of DIC and fatal septic shock at 10 times lower doses of *E coli* than in control animals. On the other hand, infusion of activated protein C in these experiments prevented the *E coli*–induced development of DIC, organ failure, and death. Increased plasma levels of C4bBP during septicemia (due to the acute phase character of this protein) may induce a relative deficiency of protein S. This hypothesis is supported by the finding that infusion of C4bBP in baboons challenged with *E coli* resulted in extensive worsening of coagulopathy and organ damage.[29]

THE CONTACT ACTIVATION SYSTEM

In septic patients, low plasma levels of factor XII and prekallikrein and high plasma levels of complexes between kallikrein and C1 inhibitor or alpha$_2$-macroglobulin and between factor XIIa and C1 inhibitor can be detected.[18,19,30] These findings indicate that the contact system is activated in septic patients. Nevertheless, experimental studies have indicated that activation of the contact system does not contribute to activation of the coagulation system in sepsis. In experimental studies of *E coli*–induced sepsis in baboons in which the contact system was blocked by the simultaneous administration of factor XII–neutralizing monoclonal antibodies, no effect was observed on the development of DIC.[31,32] However, blocking the contact activation system by this antibody resulted in a reduction of the *E coli*–induced irreversible and lethal hypotension. In these studies, the initial *E coli*–induced hypotension, occurring at 90 minutes after the *E coli* infusion, was not prevented by inhibition of the contact system, but the secondary and lethal hypotension, occurring approximately 180 minutes after the infusion of *E coli*, was not present in the baboons treated with the contact-system–inhibiting antibody. These observations suggest an important role of the contact activation system in the hemodynamic derangements of septic patients.[32] This effect is probably mediated by the generation of kinins, such as bradykinin, during activation of the contact system. Another effect of the activation of the contact system may be the effect on the fibrinolytic system. Activation of the fibrinolytic system can be achieved by plasminogen activator activity that results from activation of the contact system,[33] but neither the precise mechanism of this pathway nor its importance in sepsis has been elucidated. In conclusion, activation of the contact system in septic patients does not appear to contribute to the activation of coagulation, but seems to play an important role in the development of

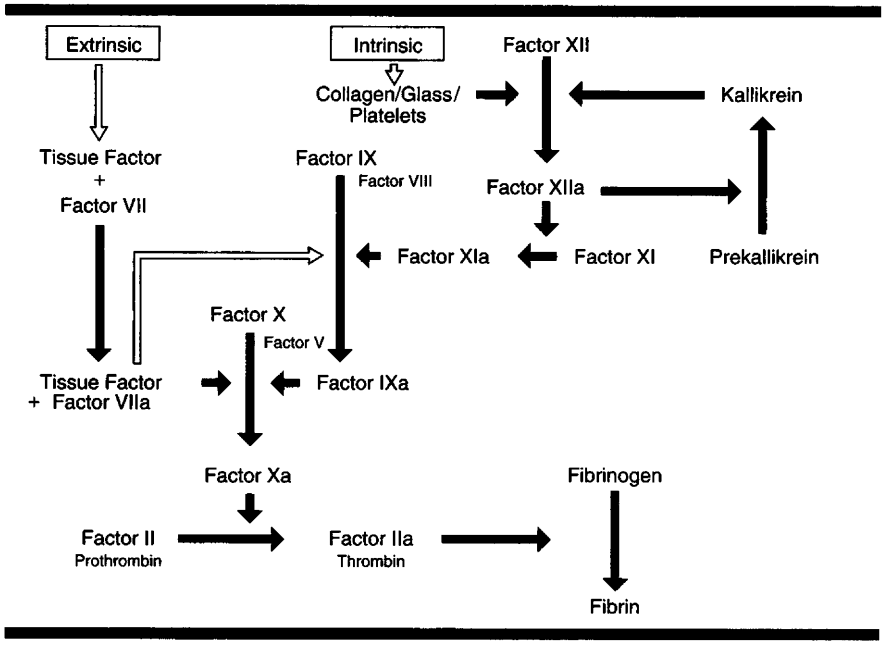

Fig 2.—The coagulation system. Activation of the intrinsic or the extrinsic pathway results in the generation of thrombin and ultimately in fibrinogen-to-fibrin conversion. The tissue factor–factor VIIa complex is also able to directly activate factor IX, which may be an important connecting link between both pathways.

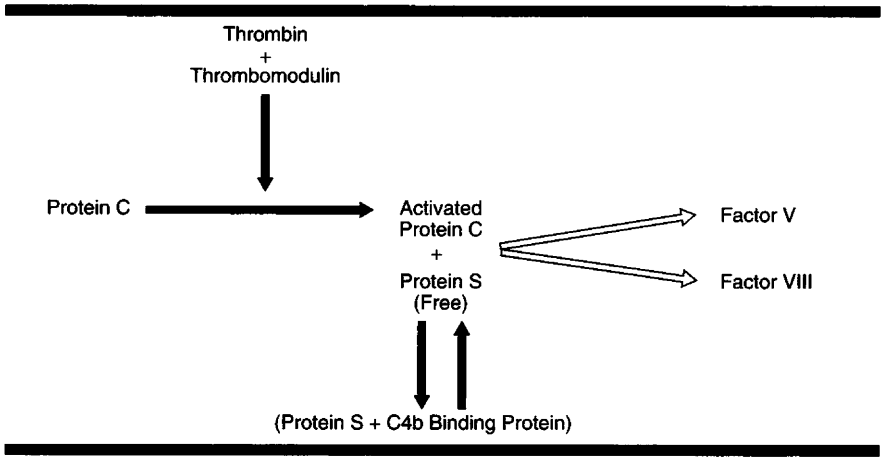

Fig 3.—The protein C–protein S system. Activated protein C and its cofactor, free protein S, are potent inhibitors of coagulation factors V and VIII.

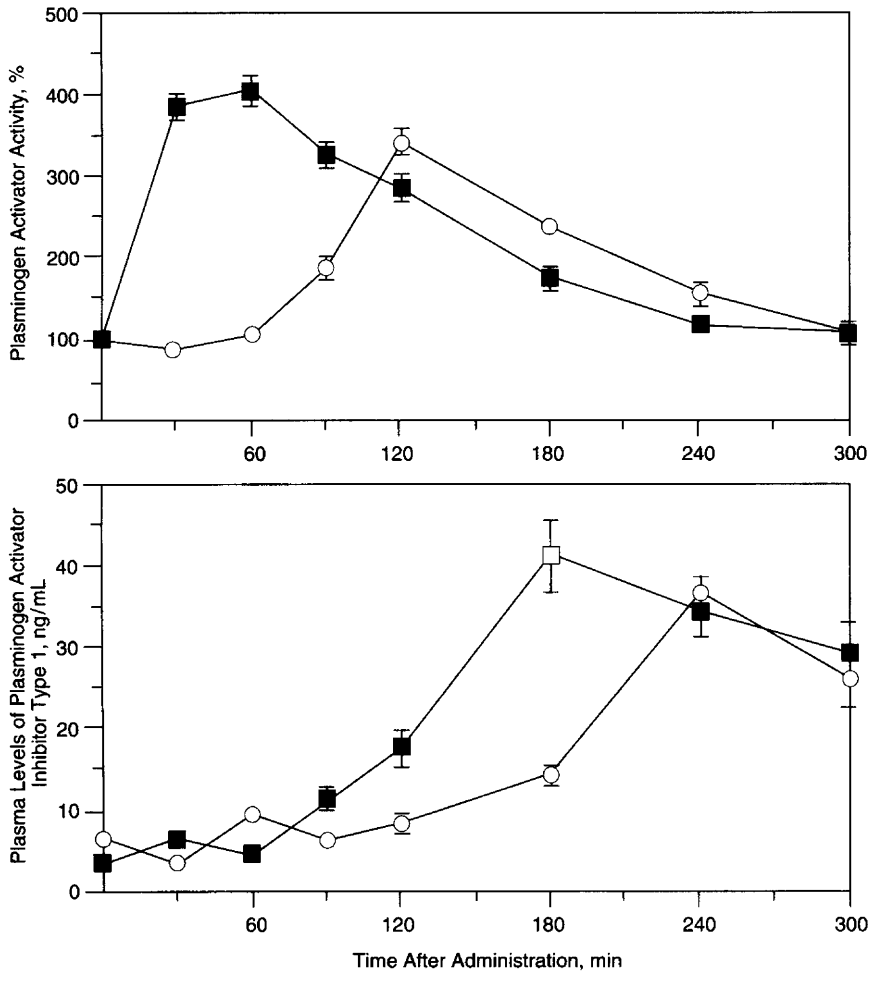

Fig 4.—Plasminogen activator activity (upper panel) and plasma level of plasminogen activator inhibitor type I (PAI-1, lower panel) after intravenous injection of endotoxin or tumor necrosis factor–α (TNF-α) in healthy volunteers. Six healthy volunteers were infused with US standard endotoxin (EC-5) at a bolus dosage of 2 ng/kg[9] (circles) and another six healthy volunteers received a bolus dose of recombinant TNF-α at a dosage of 50 μg/m² (squares).[35] Mean values ±SD are given. The increase in plasminogen activator activity is statistically significant from 90 to 180 minutes and from 30 to 180 minutes after the administration of endotoxin and after the administration of TNF-α (compared with baseline levels), respectively. Plasma levels of PAI-1 are statistically significant enhanced from 180 minutes after endotoxin administration and from 90 minutes after the administration of TNF-α (compared with baseline levels), respectively. The fibrinolytic system is initially activated, but subsequently becomes completely suppressed by the increase in plasma levels of PAI-1.

hypotension and possibly is involved in the activation of the fibrinolytic system.

THE FIBRINOLYTIC SYSTEM

In septic patients with DIC, low plasma levels of the fibrinolytic proteins and inhibitors and increased plasma levels of fibrin degradation products indicate extensive activation of the fibrinolytic system, which is traditionally believed to be secondary to the activation of coagulation.[1] Clinical studies in septic patients have suggested that the fibrinolytic system becomes initially activated and subsequently inhibited.[34] These observations were confirmed in experiments in which healthy volunteers were injected with either endotoxin or TNF-α (Fig 4).[9,35,36] Immediately following the endotoxin-induced increase in TNF-α levels (between 60 and 90 minutes after the infusion of endotoxin) or directly following the injection of TNF-α, a strong increase in plasminogen activator activity was detected. This activity was related to the increase in both tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). The plasminogen activator activity observed resulted in the conversion of plasminogen to plasmin, as reflected by enhanced levels of plasmin–alpha$_2$-antiplasmin complexes. One hour after the onset of the increase in fibrinolytic activity, the plasminogen activator activity and the plasmin generation rapidly declined, concurrently with the appearance of increased plasma levels of plasminogen activator inhibitor type 1 (PAI-1). Ultimately, the fibrinolytic activity was completely inhibited at 3 to 4 hours after the onset of endotoxemia. Comparing these observations with the kinetics of the activation of the coagulation system, it appears that, at the time of maximal endotoxin-induced coagulation activation (4 to 5 hours), the fibrinolytic system has already been offset, mainly due to high levels of PAI-1. That this remarkable imbalance between the activation of coagulation and the activation of fibrinolysis may result in an inadequate degradation of the fibrin that is deposited following activation of the coagulation system.[37] The temporal relationship between the appearance of TNF-α and the increase in fibrinolytic activity suggests that TNF-α is a mediator of this effect. A role of other cytokines, such as interleukin 1, in the initiation of fibrinolytic activity upon endotoxemia is suggested by in vitro studies,[38] but remains to be established in vivo. The important role of TNF-α was confirmed in studies of chimpanzees that were injected with endotoxin and in which the endotoxin-induced TNF-α release was blocked by the simultaneous administration of pentoxifylline (which is able to block TNF-α expression).[14] In these experiments, there was no activation of the fibrinolytic system after the endotoxemia. The observation that the increase in fibrinolytic activity occurs within minutes after the increase in TNF-α plasma levels suggests that this increase is caused by the release of plasminogen activators (t-PA and u-PA) from the endothelial cells of the vessel wall rather than by increased synthesis and that this increase is not dependent on the activation of the coagulation system. In experiments in which the endotoxin-induced activation of coagulation was blocked by monoclonal antibodies that inhibit activation of the extrinsic route of coagulation, the endotoxin-induced effects on fibrinolysis were unaffected,[14,39] which further indicated that the fibrinolytic response to endotoxin can be uncoupled from the activation of coagulation. In conclusion, endotoxemia results in a rapid activation and subsequent, PAI-1–mediated inhibition of the fibrinolytic system. The response of the fibrinolytic system to endotoxin is mediated by TNF-α and appears to be in imbalance with the activation of coagulation. This may explain the inadequate removal of intravascular fibrin deposition in sepsis.

CONCLUSION AND THERAPEUTIC IMPLICATIONS

The mechanisms involved in the development of DIC in sepsis have recently become more clear. Clinical and experimental studies have identified important mediatory roles of endotoxins and TNF-α.[5,9,11,12] Activation of the coagulation system occurs by activation of the extrinsic route,[14,24] probably by TNF-α–induced tis-

sue factor expression on the surface of activated monocytes and possibly by exposure of subendothelially localized tissue factor to the circulating blood. The intrinsic (contact-system dependent) route of coagulation activation appears not to be of importance for the activation of blood coagulation, but seems to be involved in the induction of hypotension[32] and may play a role in the activation of the fibrinolytic system. The procoagulant effects of TNF-α seem to be amplified by impaired function of the protein C–protein S inhibitory pathway, resulting from downregulation of thrombomodulin and increased serum levels of the protein S binding factor C4bBP.[28,29] An imbalance between the fibrinolytic and the coagulation system (ie, PAI-1–induced suppression of fibrinolysis during ongoing activation of coagulation) may further contribute to intravascular fibrin deposition.[35]

This increased knowledge of the various pathogenetic mechanisms of coagulation activation and fibrinolysis in sepsis may have therapeutic implications. Intervention at the level of endotoxins or cytokines (eg, by specific monoclonal antibodies) may result in treatment or prevention of DIC (and other derangements) in septic patients. Recently, studies of septic patients treated with monoclonal antiendotoxin antibodies have shown a possible beneficial effect of this approach, although the results have provoked considerable controversy.[40,41] Clinical studies investigating the effect of the neutralization of various cytokines (eg, by monoclonal anti-TNF-α antibodies or by recombinant interleukin 1 receptor antagonists) are currently ongoing. New strategies more specifically aimed at the treatment or prevention of DIC may include inhibition of the extrinsic pathway of blood coagulation (eg, by anti–tissue factor antibodies or by anti–factor VIIa antibodies). Inhibition of thrombin by specific thrombin inhibitors (such as recombinant hirudin or hirudin analogues) might be a useful option as well, but treatment with heparin (also aimed at the inhibition of thrombin) has not been proven to be effective in controlled clinical studies.[42] In addition, treatment with activated protein C concentrate may be useful in prevention or treatment of DIC. The question remains whether the proposed interventions will be effective once full-blown DIC is present. It should be stressed that novel anticoagulant strategies should be studied in controlled clinical trials that evaluate safety and efficacy in the treatment of DIC, effects on multiple organ failure and, ultimately, mortality.

Dr van Deventer is a fellow of the Royal Dutch Academy of Arts and Sciences. Dr van der Poll is supported by a grant from the Netherlands Organization for Scientific Research.

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