Sepsis/septic shock results from the excessive activation of various inflammatory systems and mediators. The release of various cytokines, hormone-like proteins that interact upon specific receptors on cells, is presumably a key event during sepsis inducing in their turn the release and activation of a number of secondary and tertiary mediators [1]. The main cytokines involved in the pathogenesis of sepsis are tumor necrosis factor-α (TNF), interleukin-1α/β (IL-1) and interleukin-1-receptor antagonist (IL-Ira), IL-6, IL-8 and other chemokines, IL-10, IL-12, and interferon-gamma (IFN-γ). Among the secondary mediators activated by cytokines is the coagulation system, which belongs to the so-called plasma cascade systems. These also include the contact, fibrinolytic, protein C and complement systems. A typical feature of plasma cascade systems is that their proteins circulate as inactive precursor molecules, for example pro-enzymes, which are activated in a waterfall or ‘cascade’-like fashion into active molecules, for example serine proteinases.

Inappropriate, mostly excessive, activation of the coagulation system frequently, if not always, occurs in animal models for sepsis, and to some extent also in humans with sepsis. In this chapter the role of coagulation in sepsis will be discussed. It is not the aim to give a comprehensive overview of clotting abnormalities in sepsis, since reviews on this topic have appeared elsewhere (see for example [2]). Rather we will focus on studies providing mechanistic insight in the role of coagulation in sepsis. As a consequence, the emphasis will be on experimental studies in animals. The contact system, which also is known as the intrinsic pathway of coagulation, will also be
summarized here. Two anti-coagulant systems, the fibrinolytic and protein C system, will also be discussed. First, a short summary of the biochemistry and the biology of these systems will be given, thereafter their role in animal models for sepsis as well as in human sepsis will be discussed. Intervention studies on the efficacy of clotting inhibitors in sepsis will be discussed in another chapter.

THE COAGULATION SYSTEM

The Common Pathway

Thrombin is the key enzyme of the coagulation system. It catalyzes the conversion of fibrinogen into fibrin, and hence has procoagulant properties. Notably, it also has anti-coagulant activities via its interaction with protein C, which is known as the thrombin paradox [3]. Thus, low concentrations of thrombin do not necessarily induce fibrin formation, but rather protect against thromboembolic events by activating protein C (Figure 1).

\[
\begin{align*}
\text{conc:} & \quad \text{effect:} \\
\uparrow & \quad \rightarrow \text{protein C activation} \quad \rightarrow \text{anti-coagulation} \\
\uparrow \uparrow & \quad \rightarrow \text{fibrin formation} \quad \rightarrow \text{coagulation} \\
\uparrow \uparrow \uparrow & \quad \rightarrow \text{TAFI activation} \quad \rightarrow \text{anti-fibrinolysis}
\end{align*}
\]

*Figure 1. The thrombin paradox. See text for further explanation.*

Thrombin is generated from prothrombin by activated factor X (FXa) in the presence of a various cofactors, i.e., factor Va (FVa), phospholipids (which serve as a surface to assemble the clotting factors), and calcium ions. Activation of factor X is considered to occur either via an extrinsic pathway (one of the components of this pathway, tissue factor [TF], is not present in plasma) or an intrinsic pathway (all components are present in plasma). The activity of the common pathway is regulated by the serine proteinase inhibitor antithrombin III (ATIII), and, to a lesser extent, by the multispecific proteinase inhibitor α2-macroglobulin (α2M). In experimental sepsis models either inhibitor indeed has been found to inhibit thrombin [4,5].