The patient study and the animal study complement each other in demonstrating that endotoxin mediated activation of the transcription factors NF-κB and AP-1 play a central role in vivo. The transcription factors nuclear factor κB (NF-κB) and activator protein-1 (AP1) are believed to control genes, which play an important role in the pathogenesis of sepsis. The NF-κB and AP1 binding activities were determined in nuclear extracts of monocytes isolated from 15 patients with sepsis (10 survivors, and 5 non-survivors). Non-survivors could be distinguished from survivors by an increase in NF-κB (p<0.001) and AP1 (p<0.05) binding activities. The increase in NF-κB and AP1 binding activities was a stronger predictor of outcome than the APACHE II score. Intravenous somatic gene transfer with an expression plasmid coding for IkBα or mutated Jun (a form of Jun capable of binding Fos, but not DNA) was used to investigate the role of members of the NF-κB and the basic-leucine zipper protein (bZIP) families in an animal model of sepsis. Intravenous somatic gene transfer with IkBα and m-Jun increased survival, decreased renal NF-κB and AP1 binding activities, decreased tissue factor expression, reduced the activation in the plasmatic coagulation system. Somatic gene transfer with an expression plasmid with tissue factor cDNA in the antisense direction (in contrast to sense or vector alone) also increased survival, decreased tissue factor expression and also reduced the activation of the plasmatic coagulation system. Somatic gene transfer with a reporter plasmid containing the functional tissue factor promoter demonstrated NF-κB and AP1-dependent stimulation by endotoxin in vivo. Thus, members of the NF-κB and bZIP families play an important role in endotoxin-mediated sepsis, partly due to regulation of tissue factor transcription.