Sepsis remains a major cause of death in intensive care units [1], commonly as the final complication of serious illness, despite adequate antibiotic treatment. Has clinical science any useful new insights into this major medical problem?

The endothelium-derived relaxing factor in blood vessels, reported in 1980 [2], was established later to be nitric oxide or a nitrosothiol. The effects of nitric oxide in regulating vascular tone, platelet function, neurotransmission and host defense have been reviewed recently in this journal [3]. These findings have led to major re-evaluation of the physiological control mechanisms in the peripheral circulation in health and disease, a task by no means complete. So far deficient endothelial release of nitric oxide has been implicated in the pathogenesis of vascular disorders as diverse as hypertension, diabetes mellitus and hypercholesterolaemia [4, 5]. The endothelial or constitutive nitric oxide synthase enzyme (eNOS) continuously replaces this short-lived local regulator, with additional release in response to increased flow velocity in the vessel (shear stress), mechanical deformation or circulating vasodilators.

Excessive production of nitric oxide contributes to the clinical syndrome of gram-negative shock, by causing pathological vasodilation and reducing the force of myocardial contraction [6]. The main links in this chain of events have been established in experimental animals. Bacterial endotoxin stimulates white cells to release cytokines [7], principally tumour necrosis factor-α (TNFα), interleukins and platelet activating factor (PAF). These cytokines in turn stimulate the expression of genes for inducible nitric oxide synthase (iNOS) in the endothelium, vascular smooth muscle and myocardium, causing overproduction of nitric oxide, which increases the intracellular concentration of cyclic guanosine monophosphate (cGMP) in these and adjacent cells. Vasodilatation results through effects on a variety of ion channels. Recent work implicated the opening of ATP-sensitive potassium channels in hyperpolarizing the smooth muscle cell and dilating the blood vessel. More widespread activation of iNOS has been observed in macrophages, neutrophils, lung, liver [8], kidney and skeletal muscle. This increase in nitric oxide may be in part protective [9].

Doubts have been expressed on the validity of animal models of endotoxaemia, or indeed the role of endotoxin in the clinical syndrome [10]. The current article by Tsuneyoshi, Kanamura and Yoshimura in this issue of the journal [11] establishes in human intestinal arteries in vitro, that endotoxin stimulates nitric oxide synthase in the smooth muscle of the vessel wall, in the absence of endothelium or many white cells, and that cGMP-mediated vasodilatation occurs with a loss of responsiveness to the vasoconstrictor actions of noradrenaline. Pretreatment with glucocorticoids reduced the vascular and biochemical changes and maintained responsiveness to noradrenaline. In accord with clinical experience of endotoxic shock, late treatment with glucocorticoids (6 h after endotoxin) was ineffective.

Attempts have been made to block this deleterious pathway at various steps. Competitive antagonism of nitric oxide synthase with analogues of its substrate l-arginine restores vascular responsiveness [12] and arterial pressure in experimental endotoxaemia, but does not necessarily improve the circulatory state of animals [13–15] or patients [3, 16]. Excessive vasoconstriction in the presence of a hypodynamic heart may restore arterial pressure but in doing so may reduce cardiac output further, leading to overall haemodynamic deterioration. Many years ago this problem limited the use of noradrenaline, metaraminol and other vasoconstrictor agents. There is experimental evidence that the excessive vasoconstriction and reduction in cardiac output caused by inhibition of nitric oxide synthase can be reversed in healthy anaesthetized pigs by the addition of selective arterial vasodilators, such as the calcium antagonist nicardipine [17] or the potassium channel opening drug levromakalim [18]. These results suggested that peripheral resistance could be monitored and controlled at appropriate levels. However, it is less easy to achieve beneficial control and restore cardiac output in pigs treated with endotoxin [19].

The administration of methylene blue, the putative inhibitor of guanylate cyclase, had haemodynamic effects similar to those of inhibition of nitric oxide synthase in patients with septic shock [20].

Non-selective inhibition of nitric oxide synthase also blocks the cytoprotective effects of nitric oxide, and may aggravate tissue damage [9]. The development of drugs which specifically inhibit the inducible form of nitric oxide synthase may preserve the beneficial effects of the constitutive endothelial release of nitric oxide [3, 12, 16]. It remains to be seen whether or not this relatively selective approach will greatly improve the clinical management of established sepsis, as it ameliorates only one end result of many complex processes.

Prevention of the formation of the inducible nitric oxide synthase in vascular smooth muscle and myocardium should be more effective, but would
require early intervention or pretreatment. Antibody to the stimulatory cytokines (e.g. anti-TNFα [21] or receptor antagonists to interleukin-1 [22] or PAF [23] reduced the effects of the administration of endotoxin to experimental animals. The clinical potential of such studies is supported by the correlation of lung injury and mortality with high blood concentrations of TNF in patients with septic shock [24]. The use of high doses of glucocorticoids for clinical management of septic shock was suggested 30 yr ago [25]. Among disparate actions, glucocorticoids reduce the expression of inducible nitric oxide synthase and cytokine release [26]. However, clinical experience has been highly variable, and controlled studies of the use of glucocorticoids have shown little benefit [27]. The direct intravascular measurement of nitric oxide in patients should result in more precise understanding of the cause and effect for better clinical management [28].

These developments in the understanding of cellular mechanisms and effects have not yet led to definitive treatment for this common and serious condition. However, there is optimism that further attack on the problem of septic shock with the new methods of molecular biology and cellular physiology will be successful. Advances in gene therapy may permit regulation of the induction of nitric oxide synthase, and control of intracellular mediators in this, as in other cardiovascular disorders [29].

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References