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Review

Systemic inflammatory response syndrome

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Background Localized inflammation is a physiological protective response which is generally tightly controlled by the body at the site of injury. Loss of this local control or an overly activated response results in an exaggerated systemic response which is clinically identified as systemic inflammatory response syndrome (SIRS). Compensatory mechanisms are initiated in concert with SIRS and outcome (resolution, multiple organ dysfunction syndrome or death) is dependent on the balance of SIRS and such compensatory mechanisms. No directed therapies have been successful to date in influencing outcome.
Method This review examines the current spectrum and pathophysiology of SIRS.
Results and conclusion Further clinical and basic scientific research is required to develop the global picture of SIRS, its associated family of syndromes and their natural histories.

One of the most frequent and serious problems confronting clinicians is the management of infection and the systemic responses that it induces. From 100 000 to 300 000 patients develop bacteraemia annually in the USA[1] and shock is a complication of sepsis in almost 50 per cent of these patients, with a mortality rate of 40–60 per cent. The clinical features associated with sepsis were noted by Hippocrates in 400 BC when he remarked that 'in acute diseases, coldness of the extremities is a very bad sign'. Sepsis remains a clinical challenge for the surgeon in and out of the critical care unit. The incidence of sepsis has been increasing for the past 60 years and is the most common cause of death in critical care units in the USA and Europe. Although remarkable progress has been made in defining the pathophysiology of this disease, the terminology associated with research in the field has been confusing. In an attempt to stratify the spectrum of sepsis, a consensus conference of the Society of Critical Care Medicine and the American College of Chest Physicians was held in August 1991 to produce a series of universal definitions for the systemic inflammatory response syndrome (SIRS), sepsis and other clinical conditions related to sepsis[2] (*Fig. 1*). SIRS was developed to imply a clinical response arising from a non-specific insult and includes two or more defined variables (*Table 1*). Sepsis is defined as SIRS with a documented infection. The sequela of SIRS/sepsis is multiple organ dysfunction syndrome (MODS) which can be defined as failure to maintain homeostasis without intervention (*Figs 2* and *3*). Primary MODS is a direct result of a well defined insult, while secondary MODS develops not in direct response to the insult but as a consequence of a host response. MODS is recognized as a sequel of SIRS. While nearly all patients with sepsis develop dysfunction of one organ system, multiple organ dysfunction occurs in about 30 per cent of patients with sepsis. Similarly, MODS can be identified in over 30 per cent of patients with trauma, 24 per cent of those with acute pancreatitis and nearly 40 per cent of patients with burns.

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There is a continuum from the development of SIRS to the onset of sepsis and progression to septic shock and multiple organ dysfunction. In a prospective survey of admissions to a tertiary care facility in the USA, 68 per cent of patients met the criteria for SIRS[3]. Of these, 26 per cent developed sepsis, 18 per cent developed severe sepsis and 4 per cent developed septic shock within 28 days. The interval between the identification of SIRS and the development of sepsis was inversely correlated with the number of SIRS criteria initially identified (two, three or four). Mortality rates in that study were 7, 16, 20 and 46 per cent respectively for SIRS, sepsis, severe sepsis and septic shock. Similar trends have been identified in the Italian SEPSIS study[4]. It is important to note that identification of SIRS alone in a patient in the intensive care unit has a poor specificity for predicting the development of sepsis and septic shock[5]. However, there is an increasing incidence of organ system failure as

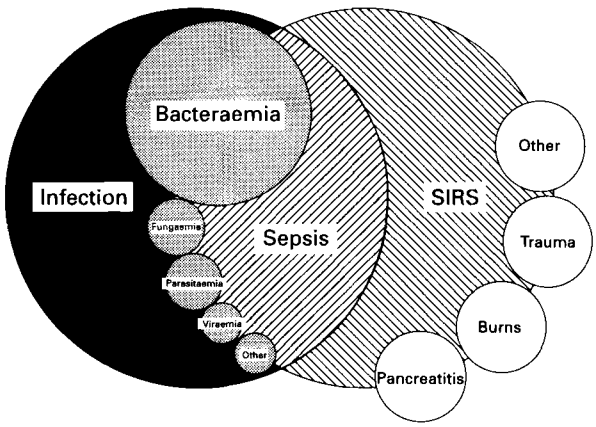

Fig. 1 The inter-relationship between sepsis, systemic inflammatory response syndrome (SIRS) and infection. Note that bacteraemia may or may not denote sepsis. ▨, Blood-borne infection. (Reproduced from reference 2 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA)

patients progress from SIRS to septic shock[3]. Another study has shown that the use of SIRS criteria in patients with trauma to predict the onset of MODS or infection is not reliable[6].

Physiology of inflammation

The innate ability of the body to defend itself is based on three elements: external barriers against invasion and tissue injury, non-specific systems against foreign pathogens and debris, and antigen-specific responses to foreign pathogens[7]. Inflammation is the body's initial non-specific response to tissue injury produced by mechanical, chemical or microbial stimuli. Inflammation is a rapid highly amplified controlled humoral and cellular response: the complement, kinin, coagulation and fibrinolytic cascades are triggered in tandem with the activation of phagocytes and endothelial cells[8]. This local response may

Table 1 Criteria for systemic inflammatory response syndrome, sepsis and multiple organ dysfunction syndrome

SIRS	Systemic inflammatory response is a characteristic clinical response manifested by two or more of the following: Temperature above 38°C or below 36°C (rectal) Heart rate above 90 beats per min Respiratory rate above 20 breaths per min or Pa_{CO_2} less than 4·3 kPa WBC count above 12 000 cells per mm^3, below 4000 cells per mm^3 or 10 per cent immature (bands) forms
Sepsis	SIRS with documented infection
Severe sepsis	SIRS with documented infection and haemodynamic compromise
MODS	A state of physiological derangement in which organ function is not capable of maintaining homeostasis

SIRS, systemic inflammatory response syndrome; Pa_{CO_2}, arterial partial pressure of carbon dioxide; WBC, white blood cell; MODS, multiple organ dysfunction syndrome. (Reproduced from reference 2 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA.)

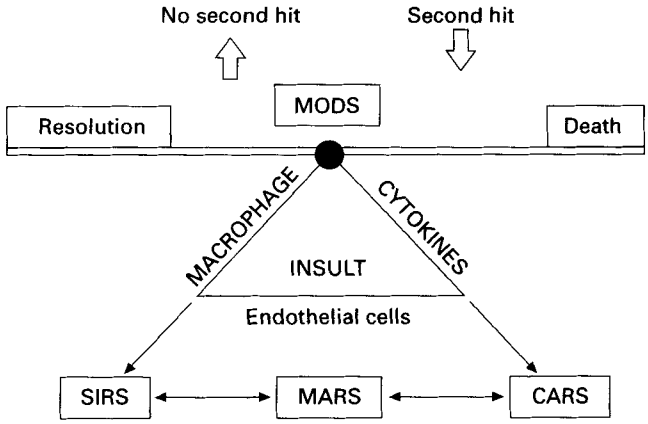

Fig. 2 The pendulum and spectrum of systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed antagonist response syndrome (MARS). Tissue insult/injury triggers a triad of systems encompassing the macrophage cytokines and endothelial cells. This results in SIRS/CARS/MARS which results in end-organ dysfunction. This can progress to multiple organ dysfunction syndrome (MODS) particularly when aggravated by a second hit (another tissue insult/injury), or can move towards resolution particularly when second hits are avoided

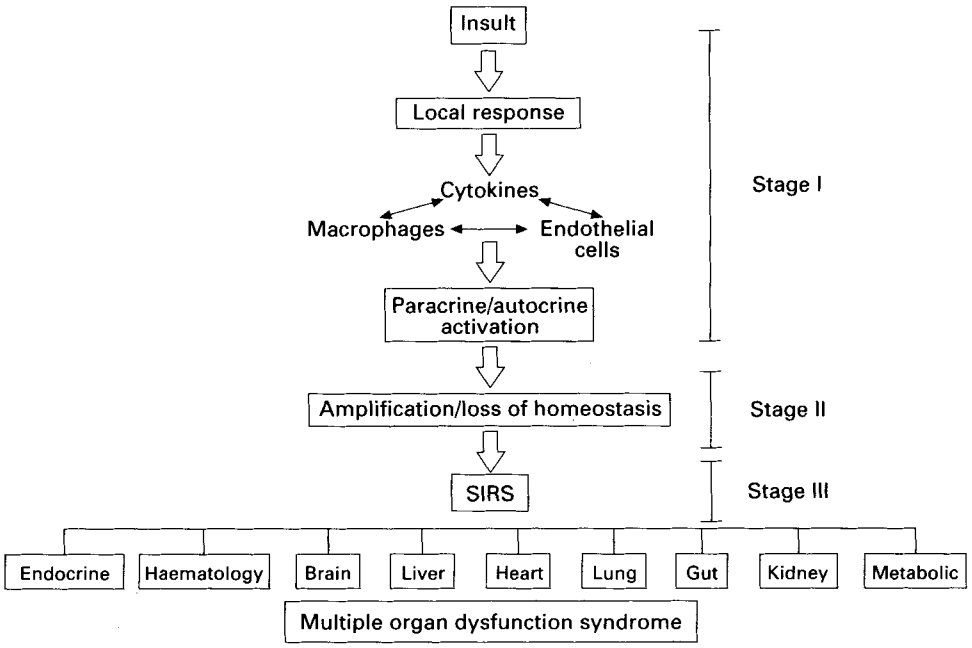

Fig. 3 Development of systemic inflammatory response syndrome (SIRS). Stage I: in response to an insult, the local environment produces cytokines which are primarily intended to evoke an inflammatory response, promote wound repair and recruit the cells of the reticuloendothelial system. In stage II, small quantities of cytokines are released into the circulation to enhance the local response. Macrophages and platelets are recruited and growth factor production is stimulated. The acute-phase response is tightly controlled by a simultaneous decrease in proinflammatory mediators and release of endogenous antagonists. This continues until the wound is healed, the infection has resolved and homeostasis is restored. Occasionally homeostasis is not re-established and stage III (SIRS) develops. The sequela of SIRS/sepsis is multiple organ dysfunction syndrome

be considered benign as long as the inflammatory process is regulated appropriately to keep cells and mediators sequestered. There are four major events in the inflammatory process: vasodilatation, increased microvascular permeability, cellular activation/adhesion and coagulation. Vasodilatation and increased microvascular permeability at the site of injury increase locally available oxygen and nutrients, and produce heat, swelling and tissue oedema. The local haemodynamic changes give rise to the four classical symptoms associated with local inflammation: rubor (erythema), tumor (oedema), calor (heat) and dolor (pain). The normal physiological response to stress and injury results in a series of cardiovascular changes (increases in heart rate, contractility and cardiac output) and neuroendocrine changes (increased release of catecholamines, cortisol, antidiuretic hormone, growth hormone, glucagon and insulin). There is an increased fluid requirement due to 'third spacing'. The major metabolic change that occurs in response to inflammation is an initial increase in oxygen consumption. The arteriovenous difference in oxygen content will remain normal provided oxygen delivery is maintained; however, anaerobic metabolism will ensue if the body fails to meet the oxygen deficit[9–11]. Concurrent with the increased metabolic responses, there is a fall in systemic vascular resistance. Unless a second insult occurs, the peak effect of these local and systemic physiological changes occurs within 3–5 days after the initial stimulus and abates by 7–10 days. Clinically, a progressive decrease in 'third space' fluid requirement, and a downward trend in pulse and temperature followed by spontaneous diuresis, herald an uncomplicated and improving clinical course.

Cytokines are the physiological messengers of the inflammatory response and the principal molecules involved are tumour necrosis factor (TNF) α, interleukins (IL-1 and IL-6), interferons and colony stimulating factors (CSFs). Polymorphonucleocytes (PMNs), monocytes/macrophages and endothelial cells are the cellular effectors of the inflammatory response. Leucocyte activation leads to increased leucocyte aggregation and tissue infiltration within the microcirculation where these leucocytes (PMNs and macrophages) undergo a respiratory burst, and increase their oxygen consumption and production of cytokines and other inflammatory mediators[12]. Endothelial cells exposed to this milieu of humoral and leucocyte-derived factors also become activated, and commence the expression of several adhesion molecules and receptors on their surface along with the synthesis and secretion of additional cytokines and secondary inflammatory mediators, including prostaglandins, leukotrienes, thromboxanes, platelet activating factor (PAF), oxygen free radicals, nitric oxide and proteases (cathepsin, elastase). Many of these secondary inflammatory mediators are also produced by leucocytes. The presence of activated endothelial cells and the enhanced cytokine milieu results in activation of the coagulation cascades which leads to local thrombosis minimizing blood loss and the walling off of injured tissues, thus attempting physiologically to isolate the inflamed areas.

Pathophysiology of systemic inflammatory response syndrome

Osler said 'patients die not of their disease, they die of the physiological abnormalities of their disease'. Localized inflammation is a physiological protective response which is generally tightly controlled by the body at the site of injury. Loss of this local control or an overly activated response results in an exaggerated systemic response which is clinically identified as SIRS. SIRS may be initiated by infection (viruses, bacteria, protozoa and fungi) or by non-infectious causes such as trauma, autoimmune reactions, cirrhosis and pancreatitis (*Fig. 1*). In a recent article, Bone[13] proposed that there were three stages in the development of SIRS (*Fig. 3*). In Stage I, in response to an insult, the local environment produces cytokines which are primarily intended to evoke an inflammatory response, promote wound repair and recruit the cells of the reticuloendothelial system. In Stage II small quantities of cytokines are released into the circulation to enhance the local response. Macrophages and platelets are recruited and growth factor production is stimulated. An acute-phase response is initiated and is tightly controlled by a simultaneous decrease in proinflammatory mediators and release of endogenous antagonists. These mediators keep the initial inflammation response in check both by downregulating cytokine production and by counteracting the effects of cytokines already released. This continues until the wound is healed, the infection resolved and homeostasis is restored. Occasionally homeostasis is not re-established and Stage III (SIRS) develops (*Fig. 3*). With the failure of homeostasis, a massive systemic reaction begins. The predominant effects of cytokines become destructive rather than protective. The flood of inflammatory mediators triggers numerous humoral cascades and results in sustained activation of the reticular endothelial system with loss of microcirculatory integrity and insults to various distant end organs (*Figs 3* and *4*).

Although flow and permeability changes at the local area increase nutrient delivery, uncontrolled systemic vasodilatation produces a sustained decrease in systemic vascular resistance and hypotension, while increased systemic vascular permeability results in significant extravascular third spacing. Coupled to these events there is depression of myocardial contractility which may be due to the effect of paracrine nitric oxide production and coronary non-occlusive microvascular damage and myocyte injury[14]. These phenomena make it difficult to volume resuscitate a hypotensive patient adequately. In combination, the loss of peripheral vascular tone and the loss of volume into extravascular spaces negate the normal homeostatic response necessary to maintain oxygen delivery and correct the abnormal arteriovenous difference in oxygen content[10,15]. The inability physiologically to correct these adverse responses results in end-organ hypoperfusion, oedema, initiation of anaerobic metabolism and end-organ dysfunction.

Early in the SIRS process, large numbers of leucocytes become adherent to the activated endothelial cells of the vessel wall and can interrupt the microcirculatory flow[16]. Leucocyte adherence is partially related to an increase in the number of adhesion molecules present on the endothelial cells. TNF-α, IL-1 and many other inflammatory mediators trigger endothelial cells to express new or increased numbers of adhesion molecules. In addition to the mechanical interruption of microcirculatory flow, activated leucocytes can damage adjacent endothelial cells and the surrounding extravascular tissue. TNF-α and IL-1 are considered primary proinflammatory mediators and induce a range of secondary proinflammatory mediators called chemokines.

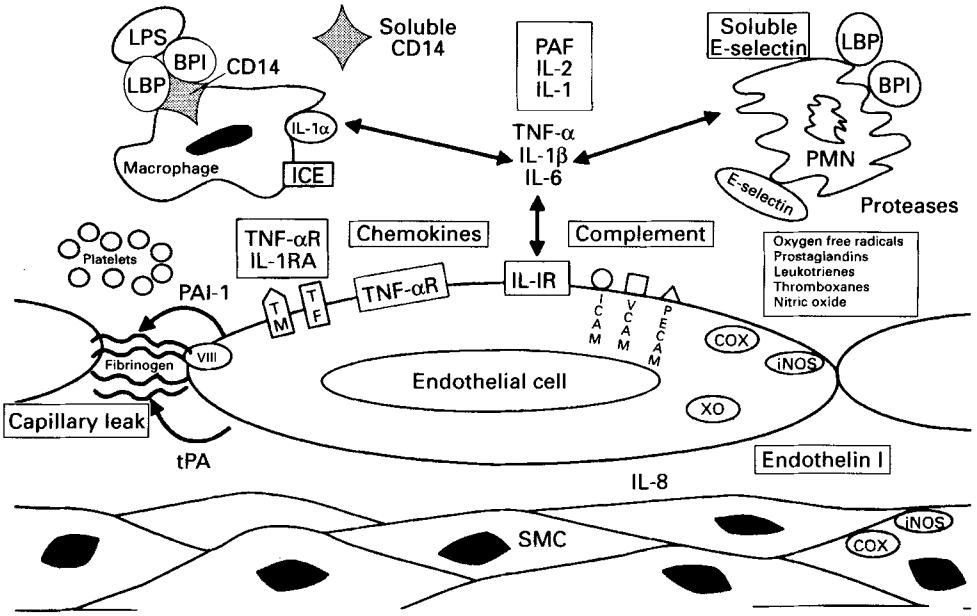

Fig. 4 The cellular biology of systemic inflammatory response syndrome. Lipopolysaccharide (LPS) can interact with lipopolysaccharide binding protein (LBP) and bactericidal/permeability increasing protein (BPI). LBP in turn interacts with the LPS receptor CD14 inducing cytokine expression. Tissue insult/injury triggers a triad of effector systems: macrophages, cytokines and endothelial cells. The principal cytokines are tumour necrosis factor (TNF) α, interleukin (IL) 1 and IL-6. Polymorphonucleocytes (PMNs), macrophages and endothelial cells are the cellular effectors of the inflammatory response. Endothelial cells exposed to this milieu of humoral and leucocyte-derived factors also become 'activated' and commence the expression of several adhesion molecules and receptors on their surface and the synthesis/secretion of additional cytokines and secondary inflammatory mediators. ICE, interleukin converting enzyme; TNF-αR, TNF-α receptor; IL-1R, IL-1 receptor; IL-1RA, IL-1 receptor antagonist; PAF, platelet activating factor; TM, thrombomodulin; TF, tissue factor; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule 1; PECAM, platelet–endothelial cell adhesion molecule; COX, cyclo-oxygenase; XO, xanthine oxidase; iNOS, inducible nitric oxide synthase; SMC, smooth muscle cell

Two major groups of chemokines have been categorized, the CXC subfamily which is chemotactic for neutrophils, and the CC subfamily which is chemotactic for monocytes[17].

Activated endothelial cells express multiple factors (e.g. tissue factor, platelet–endothelial cell adhesion molecule, thromboxane (TX) A_2) which convert their local environment from a neutral coagulant environment to a procoagulant one. In addition, TNF-α triggers the coagulation cascades by activation of the extrinsic pathway[18]. Endotoxin triggers both the coagulation and fibrinolysis cascades[19]. Factor XII has a central role in the pathogenesis of septic shock activated by the peptidoglycan residues and technoic acid from the cell wall of Gram-positive organisms as efficiently as by lipopolysaccharide (LPS) and lipid A from Gram-negative organisms[20]. Factor XIIa triggers both the intrinsic coagulation pathway through activation of Factor XI, and induces both endothelial cells and macrophages to produce tissue factor, which in turn activates the extrinsic coagulation pathway. Antibodies to tissue factor prevent LPS-induced disseminated intravascular coagulation in rabbits[21]. Endotoxaemia causes an increase in the levels of tissue plasminogen activator (tPA) in plasma which is rapidly counterbalanced by the release of plasminogen activator inhibitor (PAI) 1[22]. In sepsis, plasma levels of protein C and antithrombin III decrease and there are increased plasma levels of PAI-1. Plasma thrombomodulin, which is derived from degradation of endothelial cell membrane thrombomodulin, is also increased in SIRS[23]. The multiple actions of thrombin and the failure of natural inhibitory mechanisms, such as antithrombin III, protein S, protein C and plasma fibrinolysis inhibitors, also contribute to this process[24]. This procoagulant environment coupled to endothelial cell injury predisposes to the development of excessive microthrombi, further obstructing local blood flow and exacerbating end-organ dysfunction.

These potentially destructive systemic and regional responses in SIRS (increased peripheral vasodilatation, excessive microvascular permeability, accelerated microvascular clotting, leucocyte/endothelial cell activation) contribute to the development of profound pathophysiological changes in the various organs, and are considered the major aetiological factors in the development of septic shock, disseminated intravascular coagulation[25], adult respiratory distress syndrome (ARDS) and other end-organ dysfunction leading to MODS. Linked to these end-organ failures are the metabolic and nutritional effects of an activated cytokine milieu which produces fever, hypermetabolism, anorexia, protein catabolism, cachexia, and altered fat, glucose and trace mineral metabolism[26]. These processes are accelerated if a second insult such as shock, infection or ischaemia follows the initial injury.

Mediators of systemic inflammatory response syndrome

The mediator response in SIRS may be divided into four phases based on the cytokine/cellular response: induction,

triggering of cytokine synthesis, evolution of cytokine cascade and elaboration of secondary mediators with ensuing cellular injury. Of the multitude of mediators operating in SIRS/sepsis, the three most influential appear to be TNF-α, IL-1 and IL-6. Raised serum levels of TNF-α and IL-6 are seen in subjects challenged with endotoxin and in patients with sepsis[27,28]. Whereas absolute levels of TNF-α and IL-6 are crudely predictive of death from septic shock, persistence of TNF-α and IL-6 in serum is highly predictive of the development of MODS and death[29,30]. The deleterious host response to infection has been dissected extensively with regard to Gram-negative bacterial sepsis and endotoxaemia leading to cytokine release. Specific attention has been directed toward TNF-α, IL-1 and IL-6 because their release has been most closely associated with morbidity and death[28]. IL-6 also appears to be associated with the host septic response, probably being released in response to secretion of either TNF-α, IL-1 or both cytokines. Abrogation of IL-6 using IL-6 antibodies has been associated with improved survival in animal models of Gram-negative bacterial sepsis or in models in which TNF-α is infused. Infusion of IL-6 itself does not have any effect. Similarly, although direct injection of IL-8 does not produce adverse effects, raised levels of this cytokine have been demonstrated following a challenge of either Gram-negative bacteria or endotoxin in experimental models, but a great deal of information suggests that this cytokine acts to potentiate the effects of other mediators.

The events following endotoxin exposure provide a good model on which to discuss the four phases of SIRS. Endotoxin, shed from the bacteria as they multiply or die, is one of the most powerful triggers of SIRS by stimulating phagocytic cells, particularly macrophages, to synthesize TNF-α and IL-1, to activate the complement/coagulation cascades and to induce endothelial cell activation. Cytokines are not stored and their synthesis requires gene transcription or translation of messenger RNA (mRNA). In the baboon, after exposure to endotoxin, serum levels of TNF-α peak at 1·5 h, IL-1β at 3 h and interferon (IFN) γ at 6 h[31]. In humans, infusions of either endotoxin, TNF-α or IL-1 cause myalgia, chills, headache, nausea and tachycardia following which cardiac output increases and systemic vascular resistance falls[32]. These symptoms begin 90–120 min after endotoxin exposure, concurrent with the time TNF-α levels rise. In contrast, these symptoms occur almost immediately after TNF-α infusion. Although some investigators have identified the presence of raised IL-1 levels after endotoxin exposure, this is not a consistent finding. Similarly, increased IFN-γ concentrations have not been demonstrated after an infusion of endotoxin in humans. These studies have been extended to profile the role of cytokines in patients who develop sepsis. Raised levels of TNF-α, IL-1, IL-6, IL-8 and IFN-γ have been reported to occur in groups of patients with sepsis, but the pattern of cytokine abnormalities in each individual may not be similar to that which would be expected based on data obtained from numerous animal studies[28]. Furthermore, the correlation of raised specific cytokines with death has not been demonstrated uniformly. In addition to the circulating levels of cytokines there are increased serum concentrations of cytokine antagonists (soluble TNF-α receptor and IL-1 receptor antagonist) and antiendotoxin core antibodies in patients with SIRS; these antagonists were present at concentrations 30–100 000-fold greater than their respective cytokines[33]. There are increased complement levels in sepsis, and these have been associated with fatal outcome in both Gram-positive and Gram-negative septic shock[34–36]. Survivors of SIRS/sepsis show improvement over the first 72 h in high molecular weight kininogen concentrations and higher than normal Factor V values compared with non-survivors. Persistently low serial Factor XII, high molecular weight kininogen and Factor V are associated with a poor prognosis[37]. Enhanced levels of C-reactive protein are seen in SIRS/sepsis and a decrease in C-reactive protein level precedes clinical resolution of the condition[38].

Endotoxin

The Gram-negative bacterial wall consists of inner and outer membranes, the latter of which contains many proteins as well as LPS. LPS consists of three regions: the O antigen polysaccharide, the core and the lipid A regions. The lipid A region is considered to be responsible for the majority of the toxicity. LPS can interact with mammalian cell membranes by several different types of receptor, including CD11/18, CD14, the acetyl-low density lipoprotein scavenger receptor, other less well defined membrane proteins and by non-specific cell membrane lipid interactions. There is a family of serum proteins which possesses LPS binding sites, of which lipopolysaccharide binding protein (LBP) and bactericidal/permeability increasing protein (BPI) are the most researched[39,40]. Interaction of LPS with CD14 receptors requires the LPS first to bind to LBP[41]. CD14 response to LPS–LBP complex is enhanced compared with that to LPS alone. The enhancing effect of LBP provides an early warning mechanism for the presence of low concentrations of endotoxin. Blockade of CD14 offers an additional therapeutic option in controlling the cytokine response[42]. BPI binds to LPS and prevents macrophage activation, and is protective in rodent models of lethal endotoxaemia[41]. A soluble CD14 receptor has been identified and probably participates in all phases of SIRS with its ability to induce LPS sensitivity in cells normally insensitive to LPS (e.g. smooth muscle cells)[43].

Tumour necrosis factor α

Various cells of the reticular endothelial cell system, such as monocytes, pulmonary macrophages, hepatic Kupffer cells and peritoneal macrophages produce TNF-α[44]. The expression of TNF-α is tightly controlled both at transcriptional and translational levels. The half-life of circulating TNF-α is short, 14–18 min, and it is degraded in several organs including the liver, skin, gastrointestinal tract and kidney. Specific receptors for TNF-α are found on a wide variety of cells and a maximal biological response is elicited by occupancy of as few as 5 per cent of these receptors[45,46]. The systemic and tissue-specific cellular mechanisms of TNF-α are dependent on its direct effects as well as the release of other soluble mediators from host cells. It elicits the release of neutrophils from the bone marrow and initiates neutrophil margination by inducing expression of adhesion molecules, promoting their transendothelial passage and activation (degranulation, production of superoxides and release of lysozymes). TNF-α promotes differentiation of monocytes and macrophages, and induces the activation of macrophages. It stimulates the synthesis of acute-phase proteins and activates the common pathway of the coagulation and complement systems. TNF-α produces a dose-dependent

increase in endothelial procoagulant activity and may inhibit thrombomodulin expression at the endothelial cell surface. It induces IL-1 release from endothelial cells and macrophages, while IL-1 subsequently stimulates the biosynthesis of other cytokines. The presence of IL-1 and other cytokines appears to enhance the sensitivity of tissues to the effects of TNF-α[47]. Exogenous administration of pharmacological doses of TNF-α to experimental animals evokes the pathophysiological events associated with SIRS[48]. In an overwhelming bacterial sepsis model in baboons, passive immunization with a monoclonal antibody to TNF-α before the bacterial challenge confers complete protection against both shock and death. Levels of IL-1β and IL-6 are also attenuated[31]. Passive immunization of mice with anti-TNF-α prevents lethal endotoxaemia[49]. C3H/HeJ mice, which are genetically deficient in the ability to synthesize TNF-α, tolerate lethal doses of endotoxin with minimal effects[50].

Interleukins

IL-1 appears to be released either in parallel or in response to TNF-α secretion[51]. Abrogation of the effects of endotoxin or TNF, by specific antibodies, reduces IL-1 levels and concurrently decreases the mortality rate in experimental animal models. Animal studies in which improvement in survival occurs after blockade of IL-1 activity by use of an IL-1 receptor antagonist (IL-1RA) have provided strong evidence supporting an important role of IL-1 in deleterious effects during Gram-negative bacterial sepsis[52]. Monocytes and tissue macrophages are the primary sources of IL-1. IL-1 consists of two distinct molecules, IL-1α and IL-1β, that are structurally related polypeptides[53]. Most IL-1α remains in the cytosol in a precursor form or is associated with the cell membrane in a biologically active form. The presence of a cell-associated form of IL-1 can explain the capability of activated macrophages to induce natural killer cell cytoxicity, T cell proliferation and other functions by cellular contact in the absence of any releasable IL-1. IL-1β is cleaved by the IL-1β converting enzyme to its mature form within the cell after which it is secreted. IL-1β is also readily degraded from its precursor by trypsin, plasmin and other proteases[51]. There are two classes of high-affinity IL-1 receptors described and tissue distribution varies from 100 to 10000 receptors per cell. Patients with sepsis have greatly enhanced expression of type II IL-1 receptor mRNA and cell surface receptors, and have raised levels of soluble IL-1 receptors which may represent a mechanism of regulating IL-1 activity in sepsis[54]. Both IL-1α and IL-1β have a short half-life of 6–10 min. IL-1α and IL-1β have not been detected in the circulation of human volunteers who received endotoxin intravenously, whereas TNF-α and IL-6 were detected readily[55]. The absence of IL-α during inflammation is consistent with its primary role as a membrane-bound cytokine principally involved in local paracrine and autocrine regulation. IL-1 is a strong inducer of granulocyte/macrophage CSF (GM–CSF), macrophage CSF and hepatic acute-phase protein synthesis. Excessive IL-1 release produces excessive margination of activated neutrophils into the vascular wall, stimulates endothelial cell procoagulant activity and increases leucocyte binding, but decreases heparan sulphate binding[56]. Unlike TNF-α, IL-1 is not directly lethal but IL-1 will reproduce many of the acute haematological and metabolic phenomena associated with severe sepsis and is equipotent in inducing the synthesis of other cytokines[44].

IL-6 is a family of at least six differentially modified phosphoglycoproteins which are released rapidly within 60 min in response to injury[28]. They act as a B cell stimulatory factor, a hybridoma/plasmacytoma growth factor, a hepatocyte stimulating factor and a cytotoxic T cell differentiation factor[57]. The prevailing subtype of IL-6 after an endotoxin challenge is a 26-kDa protein. IL-6 interacts synergistically with IL-1 to affect thymocyte proliferation, and in combination with TNF-α augments T cell proliferation and promotes PMN activation and accumulation. The temporal relationship of IL-6 appearance within the cytokine cascade suggests a strong relationship to antecedent TNF-α or IL-1 stimulation[55]. Transcription and production are enhanced in response to TNF-α and IL-1. When TNF-α or IL-1 activity is attenuated, the subsequent IL-6 response is decreased[58]. IL-6 administration does not cause haemodynamic compromise, regardless of the quantity given. IL-6 suppresses LPS-induced TNF-α production and TNF-α-induced IL-1 production. Anti-IL-6 monoclonal antibodies protect mice from lethal *Escherichia coli* infection and lethal exposure to TNF-α[59].

IL-4 and IL-8 also participate in the response to injury. IL-4 synergistically increases TNF-α or IL-1-induced antigen expression in endothelial cells, but inhibits the increased expression of adhesion molecules by TNF-α, IL-1 or IFN-γ. IL-8 is produced by the endothelial cells and is chemotactic for both neutrophils and lymphocytes. Administration of anti-IL-8 antibodies prevents neutrophil-dependent tissue infiltration and damage[60]. IL-4 enhances lymphocyte adhesion to the endothelial cell. It regulates growth and differentiation of T cells. IL-4 induces antigen expression on macrophages and suppresses IL-8 expression from stimulated monocytes but not from stimulated fibroblasts or endothelial cells.

IFN-γ promotes the release of TNF-α, IL-1 and IL-6 by augmenting the effects of endotoxin on macrophages, thereby increasing the expression of adhesion molecules and cellular receptors for TNF-α. It may act synergistically with TNF-α to produce cytotoxic and cytostatic activity, synergistically increases IL-2 promotion of TNF-α release and promotes B cell activation to increase antibody production. IFN-γ enhances adhesion of lymphocytes to endothelial cells, induces marked morphological changes in endothelial cells, and encourages PMN activation and accumulation. IFN-γ enhances the phagocytic activity of PMNs and macrophage microbial function. IFN-γ antagonizes the actions of GM-CSF. GM-CSF stimulates PMN phagocytosis, degranulation and cytotoxicity. In addition it promotes maturation of macrophages and enhances their activity.

Cells

Endothelium

Because of its position, the endothelium both mediates and modulates the inflammatory and immunological responses in SIRS. The endothelium regulates the microvasculature, reacting to the metabolic needs of the tissue; it is essential in organ autoregulation and in the responses of these microvasculatures to changes in local blood flow through an extensive array of endogenously produced vasoactive factors[61]. The endothelium regulates intravascular coagulation by its participation in and

separation of procoagulant pathways, inhibition of procoagulant proteins, regulation of fibrinolysis and production of thromboregulatory compounds[62]. Basal secretion of tissue factor, a procoagulant enzyme, is low compared with that of the underlying smooth muscle cells and fibroblasts. However, if stimulated or injured, the endothelial cells can increase tissue factor production by tenfold to 40-fold. The basic barrier function of the endothelium separates intravascular coagulation factors (Factor VIIa) from tissue factor in the subendothelium and also prevents exposure of platelets to the proaggregating constituents of the subendothelium, such as collagen and von Willebrand factor. Furthermore, endothelial cells produce and express on their extracellular surfaces small amounts of the proteoglycan heparan sulphate, which serves to localize and increase the intrinsic activity of antithrombin III and tissue factor pathway inhibitor where it acts as a potent inhibitor of Factor Xa and, through its interactions with Factor Xa, produces feedback inhibition of the Factor VIIa–tissue factor complex. Endothelial cells inhibit procoagulant proteins with the protein C pathway, an autoregulatory pathway that involves protein C, protein S and thrombomodulin. Besides its direct effects on activated coagulant factors, protein C_a also increases endothelial cell fibrinolytic activity by complexing with and decreasing the activity of PAI-1, thereby increasing fibrinolysis. Endothelial cells synthesize and assemble the plasminogen activators: urokinase (uPA) and tPA. *In vivo*, normal endothelial cells express tPA only. However, if stimulated by a variety of cytokines and circumstances, endothelial cells preferentially synthesize uPA and downregulate tPA synthesis. In addition to these two fibrinolytic enzymes, endothelial cells also secrete two PAIs, PAI-1 and PAI-2. Both are serine protease inhibitors and form equimolar complexes with either active uPA or tPA molecules. PAI-1 requires the presence of fibronectin in the extracellular matrix to maintain its active conformation.

The process of cell adherence, cell activation and cell migration involves an interplay between the expression of adhesion molecules by the endothelial cells, leucocyte activation and local cytokine activity[63]. The adhesion molecules involved in endothelial cell interactions with leucocytes are currently composed of three families: the selectins which govern the interaction of lymphocytes and neutrophils, the immunoglobulins which include antigen-specific receptors for T and B lymphocytes, and the integrins which are important in platelet adhesion and cell migration. The presence of the cytokines IL-1, TNF-α and transforming growth factor (TGF) β or the presence of LPS stimulates endogenous endothelial cell production of IL-1 and IL-6, and induces IL-8 secretion. IL-8 has been shown to regulate transendothelial migration of PMNs through the endothelial barrier. The release of IL-8 is associated with a change in cell adhesion molecule expression from selectins, which are shed into the circulation to integrins which allow firm binding of leucocytes. Moreover, the action of IL-8 is enhanced by the fact that IL-8 is secreted preferentially into the vessel wall and is deposited in the subendothelial matrix by the endothelial cells, giving rise to a transmural chemotactic gradient. When endothelial cells are stimulated by cytokines or thrombin, they express endothelial cell leucocyte adhesion molecule (ELAM) 1 and intercellular adhesion molecule (ICAM) 1. Once activated, endothelial cells also produce an enhancement factor, PAF, which modulates the rapid expression of these adhesion molecules. The selectin, ELAM-1, is expressed on endothelial cells within hours and binds both PMNs and monocytes. The expression of ICAM-1, a member of the immunoglobulin family, is increased by IFN-γ, IL-1 and TNF-α. ICAM-1 facilitates the adhesion of both PMNs and lymphocytes. A second molecule in this series, ICAM-2, which is partly homologous to ICAM-1, mediates the binding of T and B cells to endothelial cells. Vascular cell adhesion molecule (VCAM) 1 is another inducible endothelial surface immunoglobulin which binds both lymphocytes and monocytes. Finally, stimulated endothelial cells can express GMP-140, a surface receptor which preferentially binds platelets. The binding of platelets increases the local availability of PAF and further accelerates the endothelial cell expression of adhesion molecules.

Leucocytes

Neutrophils play a pivotal role in SIRS/sepsis-associated tissue injury. Numerous stimuli can activate neutrophils via specific receptor systems on their surface (TNF-α, IL-1, IL-8, GM-CSF, IFN-γ, leukotriene (LT) B_4, PAF, ICAM-1 and ELAM-1, C3a and C5a). Neutrophils secrete a wide variety of mediators in response to these stimuli, both proinflammatory (IL-1α and IL-1β, TNF-α, IL-6, IL-8, IFN-γ) and anti-inflammatory (TGF-β) cytokines and their antagonists (IL-1RA)[64]. PMN activation is manifested by increased β-2 integrin expression and enhanced superoxide radical generation. Upregulation of C11b correlates with serum IL-6 level[65]. Cell surface nicotinamide adenine dinucleotide phosphate oxidase is activated and large quantities of oxygen metabolites are produced. Lipo-oxygenase and phospholipases produce LTB_4 and PAF which result in further accumulation of neutrophils and enhanced endothelial cell cytotoxicity[66,67]. Neutrophils can degrade elastin and collagen I, II, III and VI, fibrinogen, fibronectin and proteoglycans through the release of a neutral serine protease which is a major component of their granular enzymes. The metalloproteases (MMP-1, MMP-2 and MMP-3) are also secreted and will digest collagen, gelatin and proteoglycans respectively. Neutrophils bear several proteins with antibacterial properties such as BPI, cationic antimicrobial protein and desmins[68]. Neutrophil rolling on the vascular endothelium is regulated in part by the neutrophil cell adhesion molecule L-selectin. In patients with SIRS, neutrophil L-selectin expression is down-regulated in a dose- and time-dependent manner by TNF-α[69]. Neutrophils contribute to a procoagulant environment within the microcirculation by activating platelet aggregation and coagulation cascades, and inhibiting fibrinolysis[70,71]. In a porcine model, a monoclonal antibody against E- and L-selectin (EL246) significantly reduces neutrophil accumulation and tissue injury, but does not attenuate deranged pulmonary and systemic haemodynamics[72]. Similarly, organ-specific injury (acute lung injury) can be attenuated by EL246[73].

Circulating monocytes move rapidly along the endothelial cell surface (3–5 l/min for the ascending aorta). The first step in monocyte recruitment is the weak attachment of both monocyte and endothelial cell selectin molecules to their opposing corresponding oligosaccharides. The monocyte selectin, L-selectin, is produced constitutively while endothelial selectin, ELAM-1, is induced by IL-1 and TNF-α. After this initial 'weak' attachment process has been initiated the second step,

'firm' attachment, in monocyte recruitment occurs with the adhesion of the monocyte integrin $\alpha_m\beta_2$ and the endothelial cell receptor ICAM-1. ICAM-1 can be induced by exposure of the endothelial cells to IL-1, TNF-α and IFN-γ. Monocyte extravasation requires endothelial cells to express monocyte chemoattractant protein (MCP) 1 at the cell to cell junction to allow diapedesis to occur along a chemoattractant gradient[74]. Once inside the intima, the monocytes amplify the MCP-1 signal by synthesizing and secreting their own MCP-1, a characteristic of tissue macrophages[75–77]. Matrix attachment of the extravasated monocytes occurs through integrin receptors and the tissue macrophages express genes for IL-1, IL-8 and superoxide dismutase[78,79].

Monocytes/macrophages carry out the fundamental protective functions of ingesting and killing invading micro-organisms. Macrophages play a central role in the immune response by presenting antigens to lymphocytes during the development of specific immunity. Migration of monocytes into different tissues appears to be a random phenomenon during homeostasis, where they undergo transformation into tissue macrophages with morphological and sometimes functional properties that are characteristic for that tissue. The life span of tissue macrophages is believed to be months. The most important functional step in the maturation of bone marrow-derived monocytes to tissue macrophages is the lymphokine-driven conversion of the normal resting macrophage to an activated macrophage[80]. These cells are generally larger, more metabolically active, and able to release soluble substances and oxidative metabolites. Activated macrophages migrate more vigorously in response to chemotactic factors released from invading micro-organisms and enter sites of inflammation more efficiently than unactivated macrophages. Although tissue macrophages are capable of phagocytosis, tissue macrophage-mediated modulation and chemoattraction of non-macrophage inflammatory cells are important activities during sepsis[81]. Once activated, macrophages are the source of numerous cytokines involved in host defence and inflammation. Activation of tissue macrophages results in the generation of reactive oxygen species, and oxidation of arachidonic acid by lipo-oxygenase and cyclo-oxygenase pathways to generate leukotrienes, prostaglandins and thromboxane. Monocytes and tissue macrophages phagocytize particulate material via at least two distinct receptors present in their plasma membrane: the immunoglobulin (Ig) G Fc receptor and the receptor for the alternate complement pathway. Phagocytosis is increased by the presence of C3B. Particles opsonized with C3b react with activated mononuclear phagocyte C3b adherence receptors to promote increased phagocytosis through the Fc and C3b receptors respectively. Phagocytosis is augmented by fibronectin.

Secondary inflammatory mediators

Arachidonic metabolites

Metabolites of arachidonic acid, particularly those of lipo-oxygenase and cyclo-oxygenase, are significant autocrine and paracrine mediators of the SIRS. Recognized early as potent vasodilators, they play an important role in the low systemic vascular resistance and hypotension that occur in septic shock. LPS, TNF-α and IL-1 all induce the release of prostaglandins from endothelial cells. The major endothelial cell-derived prostaglandin is PGI_2, a potent vasodilator. Raised PGI_2 concentrations have been found to correlate with the severity of septic shock. The abluminal release from endothelial cells is small compared with its luminal release. PGI_2 acts on smooth muscle cells via receptor-mediated activation of adenylate cyclase. The ratio of PGI_2/PGE_2 generation is lower in the microcirculation than in major vessels. With PGI_2 production, endothelial cells also generate a small amount of TXA_2, a proaggregating vasoconstrictor. A variety of other eicosanoids, such as monohydroxy, dihydroxy and epoxy derivatives of arachidonic acid, which are formed by the cyclo-oxygenase-, lipo-oxygenase- and cytochrome P450-dependent mono-oxygenation pathways, also influence vascular tone. PGI_2 inhibits platelet aggregation and adhesion, reduces thrombus formation and acts synergistically with prostaglandin PGE_2 to increase the effects of serotonin and bradykinin. PGE_2 inhibits both IL-1 production and responsiveness of thymocytes to IL-1. Low concentrations of PGE_2 stimulate TNF-α release, while higher concentrations suppress TNF-α production at a dose-dependent level; PGE_2 inhibits mitogenesis of T and B cells and acts synergistically with prostacyclin to increase the effects of serotonin and bradykinin on vascular permeability. TXA_2 induces platelet aggregation and neutrophil accumulation, increases vascular permeability and enhances permeability of single and double unit membranes. LTB_4 promotes neutrophil chemotaxis and adhesion of neutrophils to endothelium. Neutrophils have specific LTB_4 receptors. LTB_4 is weakly chemotactic for eosinophils and increases vascular permeability, either directly or through interaction with neutrophils and endothelial cells. LTC_4, LTD_4 and LTE_4 stimulate release of prostacyclin, increase vascular permeability and cause contraction of adjacent endothelial cells and a resulting increase in the diameter of interendothelial cell pores.

Nitric oxide

Synthesis of nitric oxide plays a crucial role in acute and chronic inflammatory processes, in the SIRS and in sepsis[82,83]. Nitric oxide is synthesized from the conversion of L-arginine to citrulline by at least two categories of enzyme: constitutive nitric oxide synthases (cNOS; predominantly membrane bound) and inducible nitric oxide synthases (iNOS; predominantly cytosolic) both of which are calcium- and calmodulin-dependent. Protein phosphorylation by the guanosine 3′,5′-cyclic monophosphate (cGMP)-dependent kinases, which are activated by nitric oxide-mediated increases in target cell cGMP, is the basis of many of the effects attributed to nitric oxide. Nitric oxide shares many of the vasoactive properties of prostacyclin in that it can relax smooth muscle and inhibit platelet aggregation. In the appropriate circumstances, nitric oxide can be converted in the endothelial cell to peroxynitrite, a potentially toxic molecule. Peripheral blood monocytes, alveolar macrophages, Kupffer cells and neutrophils, once stimulated, are all capable of synthesizing iNOS and producing nitric oxide[84]. Nitric oxide enhances the vasodilatation, the formation of oedema and the modulation of sensory nerve endings which are hallmarks of the inflammatory response. Inhibition of nitric oxide synthesis will reduce the degree of acute inflammation. Raised concentrations of nitric oxide are likely to come from a combination of sources: activated vascular cells, neutrophils and macrophages[85,86]. These effects can be prevented by treatment with glucocorticoids and NOS inhibitors. In endotoxic shock,

increases in nitric oxide production can be related to the level of hypotension[87]. Bacterial endotoxin induces iNOS and raised nitric oxide synthesis in venous smooth muscle cells, in the cardiomyocytes and in the endocardium, and leads to increased venous pooling and cardiac dysfunction (sepsis-related dilated cardiomyopathy)[86]. Cytokine induction of myocardial iNOS results in increased nitric oxide production and negative inotropy[88]. NOS activity is significantly higher in patients with sepsis[89].

Studies in animal models on the inhibition of NOS activity have shown a mixed picture of efficacy in the treatment of septic shock[90]. While 30 mg/kg L-nitro-monomethyl arginine will prevent endotoxin shock, 300 mg/kg will accelerate the condition. Early reports suggest that inhibition of nitric oxide is beneficial in septic shock. The benefit of inhibited NOS activity is a sustained increase in systemic blood pressure, while the adverse effects are decreased cardiac output and raised pulmonary vascular resistance[91–94]. Hepatocyte dysfunction appears to be the result of cytokine-induced production of nitric oxide (through iNOS) and cytokine release from macrophages and Kupffer cells[86]. Macrophages synthesize nitric oxide and the high concentrations of nitric oxide are responsible for the cytotoxicity of macrophages to tumour cells and bacteria[84,95]. The cytotoxicity of nitric oxide results from its interaction with iron-containing moieties in enzymes of the respiratory cycle and the DNA synthesis pathways[96].

Reactive oxygen species

Endothelial cells contain xanthine dehydrogenase/oxidase and the free radicals produced or transferred from the extracellular space under normal conditions are reduced by endothelial cell superoxide dismutase, catalase and the glutathione redox cycle. Low intracellular levels of oxygen free radicals stimulate cyclo-oxygenation of arachidonic acid. Superoxide radicals can induce vasodilatation in several tissue beds and this is thought to be mediated by the release of prostacyclin from endothelial cells. However, increased intracellular concentrations of oxygen free radicals are able to inactivate nitric oxide and can inhibit the production of prostacyclin in endothelial cells by inhibiting both cyclo-oxygenase (COX-I) and COX-II synthetases. Higher levels will result in the destruction of these enzymes. In contrast, TXA_2 synthetase is resistant to such free radical inhibition and destruction. The net effect of these interactions is vasoconstriction[97]. In addition, oxygen free radicals can lead to the formation of peroxides and, because of the difference in kinetics between the cyclo-oxygenase and peroxidase enzymes, lipid peroxides can accumulate; raised concentrations of these compounds will also destroy both COX-I and COX-II synthetases. This damage can be prevented by antioxidants. In normal physiology, a balance exists between the production of PGI_2 and TXA_2, and between nitric oxide and oxygen free radicals, which allows for the maintenance of vascular tone[98].

When tissues are injured by ischaemia or anoxia, their ability to control the metabolism of oxygen is compromised and the species that are generated activate a superoxide-dependent chemoattractant process. This leads to an influx of leucocytes which generates still more reactive oxygen species. Reactive oxygen species are involved in most types of inflammatory tissue injury and are derived predominantly from phagocytic leucocytes[99,100]. Reactive oxygen species produce cellular injury directly by oxidative degradation of essential cellular components and indirectly by altering the protease/antiprotease balance that exists between cells. Reactive oxygen species can further initiate and amplify the inflammatory process by upregulation of several proinflammatory cytokines (IL-2, IL-6 and TNF-α) and adhesion molecules (E-selectin, ICAM-1 and VCAM-1)[100,101]. The undisputed contribution of reactive oxygen species to the SIRS has prompted increasing experimental work on means to counteract their local tissue effects[102]. A preliminary report of a randomized trial of *N*-acetylcysteine in patients with established sepsis-induced ARDS suggests that the antioxidant therapy is useful[103].

Platelet activating factor

Endotoxin induces the release of PAF from macrophages, PMNs, platelets and endothelial cells. Systemically, PAF has a negative inotropic effect on the heart and lowers arterial blood pressure. PAF is a potent phospholipid inflammatory mediator that increases cell adhesion, and activates cells by direct effect or through the formation of toxic oxygen species and arachidonic acid metabolites. PAF stimulates the release of TNF-α, leukotrienes, TXA_2, and promotes leucocyte activation and subsequent free radical formation. There is growing evidence that haematological growth factors and cytokines interact with PAF, leading to amplification of mediator release in septic shock, and that PAF mediates many of the toxicities associated with TNF-α and IL-1[104,105]. Within the microcirculation, PAF encourages platelet aggregation, leading to thrombus formation, and markedly alters microvascular permeability by stimulating calcium efflux in endothelial cells, which results in retraction and loss of reciprocal contact. Specific PAF receptor antagonists provide protection against the fatal complications of endotoxic shock in animal models[106,107].

Nutrition

Severe depletion of body protein stores can result from prolonged starvation, or from hormonal or cytokine-mediated effects during critical illness[108–110]. Specialized enteral and parenteral nutrition is now a standard component of care in critically ill patients. This adjunctive therapy corrects and prevents nutrient deficiencies, attenuates the loss of body protein, enhances immune function, and beneficially modifies a body's response to illness, thereby improving clinical outcome in malnourished patients. In patients without severe head injuries, infectious complications are the most common cause of death, and are a frequent cause of morbidity and mortality. Morbidity from sepsis is significantly reduced in critically injured patients when total enteral nutrition (TEN) rather than total parenteral nutrition (TPN) is provided, implying benefits of enteral feeding on host defences[111]. A lack of enteral feeding is thought to lead to a breakdown of the gut mucosal barrier and translocation of bacteria or their products, while the use of TEN or trickle feeding prevents the deterioration in the gut's ability to prevent translocation. Preservation of the barrier function of the gut is essential in controlling sepsis-related morbidity associated with severe injury and stress. Ample experimental evidence suggests that TEN is superior to TPN in preventing many coincidental septic events and modulating the host response to ongoing sepsis that occur in critically ill patients. Immunonutrition is the term being used now to refer to the effects of nutritional

hyperalimentation on the immune system[112]. The components of immunonutrition are glutamine, arginine, omega-3 fatty acids and RNA nucleotides. Glutamine has a significant trophic effect on the gut. It is the preferred fuel source for the intestinal tract in times of stress and is a key component in preventing enterocyte loss, atrophy of the mucosa and loss of barrier function. It is also a known fuel for lymphocytes. Arginine has significant immunostimulant effects, with prevention of thymic atrophy, increased production of natural killer and helper T cells, and increased IL-2 release, which stimulates T cell activation. Long-chain omega-6 fatty acids, which are a common component of TPN and TEN solutions, are more significantly immunosuppressive than omega-3 fatty acids. The presence of omega-3 fatty acids leads to a change in the profile of prostaglandins and leukotrienes produced during stress and sepsis (omega-6 fatty acids increase PGE_2 and LTB_4 synthesis while omega-3 fatty acids increase PGE_3 and LTB_5 synthesis). The absence of RNA nucleotides has been shown to decrease the maturation and phenotypic expression of T lymphocytes, to decrease IL-2 production, to inhibit resistance to infection and to diminish T cell-based immunity. There are mixed opinions that nutritional formulae which contain immunomodulators may convey a small benefit over standard formulae. There are some data to suggest that they may be detrimental in certain subsets of patients[112].

Potential therapies

There are three points in the sequence of the pathogenesis of SIRS/sepsis at which therapy can be instituted. First, the nidus of infection can be eradicated with appropriate antimicrobial therapy, surgical drainage, or both. Second, the sepsis-associated cardiovascular metabolic and multiorgan system disturbances can be treated and, third, inhibitors of toxic mediators can be administered[113].

Anti-lipopolysaccharide

LPS comprises complex molecules composed of a polysaccharide side chain (O antigen), attached to a glucosamine-based phospholipid (lipid A) by a 'core' polysaccharide. Polyclonal antisera and monoclonal antibodies to lipid A and core regions of mutant *E. coli* have been developed and tested in clinical trials, some of which have had positive results[114] while others have been negative[115,116]. Two prophylactic studies comparing antiserum with preimmune serum in high-risk surgical patients and in neutropenic patients with cancer did not show a reduction in Gram-negative infections by the administration of antiserum[117,118]. The use of the non-toxic derivatives of lipid A, the presumed toxic moiety of the endotoxin molecule, to attenuate the response to LPS, enhances non-specific resistance to infection and induces tolerance to endotoxin[119–122].

Recently murine and human monoclonal IgM antibodies have been developed using the *E. coli* J5 mutant and have been tested for the treatment of patients with Gram-negative infections in prospective randomized double-blind multicentre trials. In an initial study with E5 murine IgM monoclonal antibody, patients with suspected Gram-negative sepsis were assigned randomly to receive either E5 antibody or placebo[123]. There was no decrease in mortality rates in patients from either group but after subgroup analysis it did appear there was a decrease in mortality rate in patients without shock at the time of entry into the study. A second study concentrating on patients with Gram-negative sepsis but no shock failed to show any benefit with E5[124]. Treatment with a second antibody, HA-1A (human), did not improve overall population survival at 28 days[125]. A subgroup of patients with Gram-negative bacteraemia showed a significantly improved survival at 28 days and this reduction in mortality rate was more pronounced in patients with shock than in those presenting without shock. Unfortunately there were more patients in the placebo arm than in the HA-1A arm who had considerably more risk factors and they received inadequate antibiotic therapy compared with the experimental patients[126]. Other therapies for blocking the LPS-induced phase are soluble CD14 receptors, anti-LPS-binding protein, anti-CD14 receptor antibodies and bacterial permeability increasing protein.

Anti-tumour necrosis factor α

As TNF-α is a primary mediator of the SIRS response, neutralization is an attractive possibility. Antibodies to TNF-α have decreased the mortality rate in models of lethal bacteraemia and, although there was a decrease in 3-day mortality rate in humans, there was no decrease in the rate between patients treated with placebo and a monoclonal antibody against TNF-α at 28 days[127–129]. There are naturally occurring proteins which represent the extracellular domains of the two TNF-α receptors. They act as natural TNF antagonists and prevent septic shock in *E. coli*-treated baboons and death in mice. A chimaeric molecule in which the soluble TNF-α receptor is linked covalently to the Fc portion of IgG has been designed and produced. With a single administration, the chimaeric molecule can significantly improve septic shock in animal models[130]. In patients with septic shock the chimaeric molecule (TNFR:Fc) did not reduce the mortality rate[131].

Anti-interleukin 1

There is a lag time between activation of TNF-α and IL-1 expression. This window of opportunity suggests that targeting IL-1 may be temporally more efficacious than targeting TNF-α. IL-1 receptor antagonists reduced mortality rates in a rabbit model of septic shock even when given after the onset of shock[132]. IL-1RA is a naturally occurring protein which binds to the human IL-1 receptor but has no agonist activity[133,134]. It must be administered in very large molar amounts in order to block IL-1 activity. There is no significant increase in overall survival time in patients treated with IL-1RA[135]. However, there is a significant increase in survival time in patients treated with IL-1RA within the first 2 days if these patients have a 24 per cent or more risk of death within 28 days. There was no benefit if the patient had a risk of death below 24 per cent[136].

Miscellaneous agents

Cytokine synthesis can be blocked at a translational level by steroids and at a pretranslational level by pentoxifylline (oxypentifylline) and amrinone. Steroids block the translation of TNF-α mRNA in macrophages. They must be administered pre-emptively to have an effect;

administration after the onset of sepsis carries no benefit[30,137–140]. Pentoxifylline and amrinone are phosphodiesterase inhibitors that lead to increased intracellular levels of adenosine 3′,5′-cyclic monophosphate which interrupts intracellular signalling[141,142]. Pentoxifylline decreases TNF-α synthesis in a murine model of endotoxic shock, while amrinone has been shown to be a more potent inhibitor of LPS-stimulated TNF-α synthesis[143–145]. In humans, pentoxifylline is able to decrease TNF-α but not IL-6 and IL-8 serum concentrations, and to decrease augmented PMN reactivity during septic shock[146,147]. Biologically-derived glucan infusions improve immune function after trauma and after high-risk abdominal surgery[148,149]. Taurolidine is considered to be a non-specific LPS antagonist. It has no beneficial therapeutic effect on the outcome of patients admitted to the intensive care unit with sepsis syndrome, using progression, resolution of organ failure and 28-day mortality rate as markers of outcome[150].

Arachidonic acid metabolites help mediate haemodynamic alterations in SIRS/sepsis[36,151–153]. Indomethacin given 1 h before or after a bolus of TNF-α blocks metabolic acidosis, shock and death in rats[154]. Similarly, ibuprofen has also been shown to be effective in animal models[155,156]. However, it has no effect in man[157]. Leukotriene inhibitors have been shown to be beneficial in septic shock[158]. Combined therapies to inhibit several components of the arachidonic acid pathways are more effective than single drug therapy in protecting animals from progressing to MODS[159,160].

Specific PAF receptor antagonists provide protection against the fatal complications of endotoxic shock in animal models[106,107]. In patients, the use of PAF antagonists has shown no benefit[161]. Activation of the kallikrein–kinin system in sepsis has long been recognized and, experimentally, bradykinin antagonists have been shown to be beneficial in Gram-negative sepsis[162].

Newer concepts in systemic inflammatory response syndrome

With failure of the single agent therapies to control SIRS, several authors have suggested that there is a fundamental misconception of the disease process within the human body. SIRS, which is proinflammatory, is only one side of a two-sided response. The other side is an anti-inflammatory response termed the compensatory anti-inflammatory response syndrome (CARS)[163]. The rationale for this theory is that many of the proinflammatory mediators, particularly the interleukins, that participate in SIRS can inhibit immune function by decreasing monocyte/macrophage, B cell and T cell function. In addition, the proinflammatory mediators can inhibit their own synthesis or enhance the synthesis of natural antagonists. Cumulatively, these responses are the body's attempt to re-establish homeostasis, and result in anergy and increased susceptibility to infection. Thus, at any one time there is a battle between the 'Ying' and 'Yang' of the inflammatory system which clinically manifests itself as SIRS, CARS or an intermediate, mixed inflammatory response syndrome (MARS). The spectrum of consequences of these responses has been termed CHAOS (Cardiovascular shock, Homeostasis, Apoptosis, Organ dysfunction and immune Suppression)[163,164]. This new set of concepts suggests that if SIRS is predominant, conventional antimediator or antagonist therapies will be of value, but if CARS is predominant, then novel immune stimulants or antiantagonist therapies will be required. To enter this algorithm, a fundamental step will be required, that of achieving a diagnosis of the systemic inflammatory state of the patient (SIRS, CARS or MARS).

Conclusion

The consensus definition of SIRS has allowed translation of several unrelated disease states into a universal process from which it will be possible to categorize, research and treat the body's normal and abnormal inflammatory response to any insult. For surgeons, it forms the basis of the physiology and pathophysiology which their patients experience and which they treat in their practice. In the past decade the cellular and humoral events of inflammation and the systemic inflammatory response that can result have been better defined, yet our overall knowledge in this field is still limited. The newer concepts of MARS, CARS and CHAOS in the natural history of SIRS testify to these limitations and suggest possible new horizons to our understanding (*Fig. 5*). At present, attempts to intervene in the cascades that participate in SIRS have met with little success. These unifocal attempts are based on our present knowledge and require pre-emptive therapy which cannot at present satisfy the clinical requirement of controlling SIRS after the cascades have been initiated. It is akin 'to closing the barn door after the horse has bolted'[165]. Furthermore, there is no evidence to refute a contention that part of the SIRS

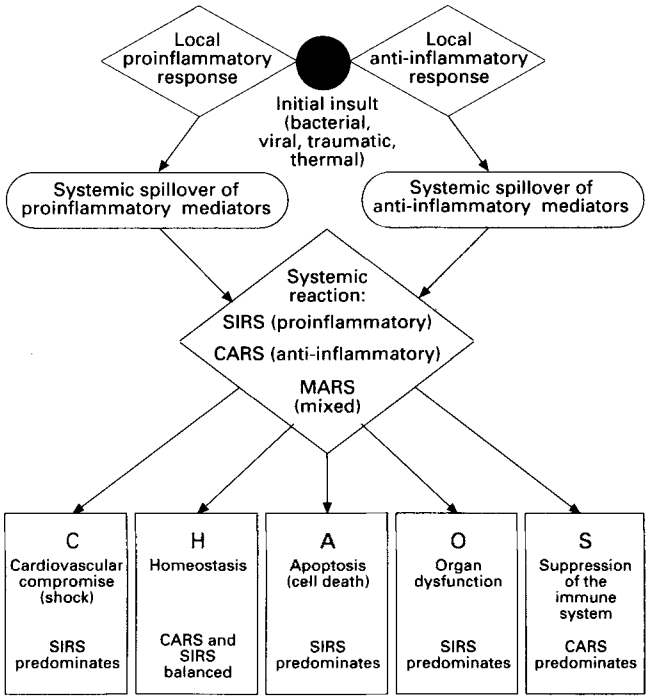

Fig. 5 The inter-relationship of systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed antagonist response syndrome (MARS) and the CHAOS (Cardiovascular shock, Homeostasis, Apoptosis, Organ dysfunction and immune Suppression) theory. Clinical sequelae of the SIRS and the CARS. (Reproduced from reference 163 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA)

response is beneficial for the patient in the longer term. Further clinical and basic scientific research will be required to develop the global picture of SIRS, its associated family of syndromes and their natural histories. Modulation of SIRS/CARS remains in its infancy.

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