The systemic responses to trauma can be divided into cardiovascular, immunological, and metabolic. The cardiovascular responses are seen immediately after a traumatic insult. The pattern of response depends on whether the insult is mainly haemorrhagic, tissue damage, or a combination of the two. The response may be quite different for penetrating vascular trauma, compared with a crush injury to a limb. The immunological, or inflammatory, consequences of trauma usually become apparent several hours or days after the initial insult, although it is increasingly clear that they may be triggered by the very early cardiovascular changes. These have been implicated in the development of multiple organ failure. The metabolic responses are of greatest importance in the longer term: after successful resuscitation and after the definitive treatment of the patient's injuries. The metabolic responses need to be taken into account during the recovery from treatment and during the rehabilitation of the patient.

The aims of this chapter are to present an overview of the physiological responses to trauma. These can be divided for practical purposes into three: cardiovascular, immunological, and metabolic. This chapter will cover the first two, while the third: the metabolic response to trauma is covered in a separate volume of the British Medical Bulletin.  

In the 1970s and early 1980s, mortality from trauma was described as following a trimodal distribution. Deaths occurred either immediately, or within the first few hours, or much later (days, even weeks, after the accident). A better understanding of the early pathophysiology of trauma and improvements in the early management of trauma patients seems to have resulted in a reduction in the early deaths. In some areas, the trimodal distribution of deaths has been lost. Continued advances in the management of trauma depend on a good understanding of the systemic responses.  

Studying the response to trauma in a clinical setting is often difficult: the urgency of resuscitation makes extensive physiological assessment impossible and the resuscitation itself will alter the responses observed. For this reason, much of our understanding of the responses to trauma comes from laboratory studies using human volunteers and animal models.
The cardiovascular response to trauma

In a physiological sense, trauma is not a single insult: it is a combination of haemorrhage, tissue injury, pain, and fear. To understand the physiology of trauma these components have often been studied in isolation.

The cardiovascular response to haemorrhage

The biphasic response to haemorrhage

Systematic research into the cardiovascular responses to haemorrhage began in the Second World War, when extensive blood donor programmes were established. It was found that a small percentage of blood donors lost consciousness following even a small haemorrhage, and that the percentage increased as the volume of venesection increased. This observation was studied by venesecting volunteers and monitoring heart rate, blood pressure, cardiac output, right atrial pressure and fore-arm blood flow. Initially, the response to haemorrhage was an increase in heart rate and total peripheral vascular resistance so that, despite a fall in cardiac output, blood pressure was maintained (Fig. 1). However, once about 1000 ml of blood had been removed, there was a sudden fall in blood pressure associated with a bradycardia and syncope. This was found to coincide with a profound increase in fore-arm blood flow and a reduction in systemic vascular resistance. These changes could be largely reversed by re-infusion of the shed blood.

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**Fig. 1** Biphasic response to haemorrhage. Faint induced by venesection showing the biphasic response in heart rate (HR), blood pressure (SBP) and systemic vascular resistance (SVR) with a gradual reduction in cardiac output (CO). Adapted from Barcroft et al.

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It appeared that the response to simple haemorrhage consisted of two distinct phases: an initial phase of tachycardia and increased vascular resistance maintaining arterial pressure, followed by a phase of decompensation with hypotension and bradycardia. These observations have been confirmed clinically, in simulated hypovolaemia, and in animal experiments. The bradycardia of haemorrhagic shock is reviewed by Secher and Bie. The precise mechanisms controlling this biphasic response to simple haemorrhage have been extensively reviewed. Only a brief outline of two of the reflexes involved will be provided here.

**The arterial baroreceptor reflex**

A relatively small haemorrhage (up to 10–15% of total blood volume (TBV)) results in an unloading of arterial baroreceptors located in the aortic arch and carotid sinuses. The result is a reduction in cardiac vagal activity and an increase in sympathetic stimulation of the heart. At the same time, there is an increase in sympathetic vasoconstrictor tone and an increase in total peripheral vascular resistance so that arterial blood pressure and perfusion to tissues critically dependent on oxygen supply are maintained despite a reduction in cardiac output.

**The 'depressor' reflex**

When blood loss exceeds a critical volume (usually around 20% TBV), hypotension and bradycardia are seen. This is due to the activation of another reflex, referred to as the 'depressor' reflex, which appears to over-ride the baroreceptor reflex. The efferent limb of this 'depressor' reflex is carried in the vagus (increased activation leading to bradycardia, which can be blocked by atropine) and the sympathetic vasoconstrictor nerves (decreased activation leading to vasodilatation). The precise nature of the afferent limb of the 'depressor' reflex is still unclear.

**The triphasic response to haemorrhage**

A recent animal study showed that after the bradycardic phase of haemorrhage there was a massive increase in heart rate as blood loss reached 44% of total blood volume. This was associated with a further reduction in mean arterial pressure.

Jacobsen and Secher observed a similar triphasic response in a series of patients in haemorrhagic shock. No patients in the bradycardic phase died, suggesting that this phase of haemorrhagic shock is reversible with prompt fluid resuscitation. However, once patients go into a phase of tachycardia and hypotension, shock may be irreversible. This third and potentially irreversible phase of haemorrhagic shock is associated with increased sympathetic activity. The precise mechanisms...
triggering this have not been clearly elucidated, but it may be related to the development of cerebral hypoperfusion and cerebral hypoxia.

**The cardiovascular response to tissue injury**

The response to tissue injury consists mainly of a pressor response: an increase in blood pressure mediated by an increase in sympathetic vasoconstrictor tone producing an increase in peripheral vascular resistance\(^{19}\). The tissue injury response is accompanied by a tachycardia: there is a suppression of the baroreflex\(^{20}\) which would normally result in a bradycardia.

A similar response is seen when the 'defence area' of the brain is stimulated electrically\(^{21,22}\). Stimulation of the 'defence area' provokes the 'defence reaction' the features of which are: (i) a tachycardia (ii) an increase in blood pressure; (iii) an increase in sympathetic efferent activity; and (iv) a relative vasodilatation to skeletal muscle with vasoconstriction in the splanchnic vasculature. In contrast to the response to haemorrhage, which preserves blood flow to vital organs, the response to injury prepares the organism for 'fight or flight' and so diverts blood away from the visceral organs to skeletal muscle. The similarities between these two responses has resulted in the suggestion that the response to tissue injury is mediated via the same pathways as the defence reaction. A more detailed explanation of the central pathways can be found in Kirkman and Little\(^{17}\).

**The cardiovascular response to combined haemorrhage and tissue injury**

Historically, haemorrhage was regarded as a complication of wound shock. When Parsons and Phemister realised that blood loss could account for wound shock they also noticed that a minor degree of haemorrhage could be fatal if associated with tissue injury\(^{23}\). This interaction was studied later by Wang et al\(^{24}\). In a canine model of haemorrhage and haemorrhage and soft tissue injury, there was a higher mortality in the haemorrhage and soft tissue injury group. As the circulating volume lost was the same in both groups they concluded that another factor was involved. In further studies, they found similar increases in mortality when sciatic nerve stimulation or soft tissue injury were added to their haemorrhage model\(^{25}\). From this, they deduced that afferent nerve stimulation was an important factor in the increased mortality of traumatic shock compared with simple haemorrhagic shock.

A variety of models has been used to study the interaction between haemorrhage and tissue injury. Figure 2 compares the cardiovascular
response to haemorrhage with and without concomitant tissue injury, modelled using hind-limb ischaemia. A number of differences are apparent. The background limb ischaemia results in a higher resting HR and MAP. It appears that there is a re-setting of the baroreceptor reflex to a higher MAP and there is also a reduction in the sensitivity of the reflex. Coote et al showed that somatic afferent nerve stimulation can modulate the baroreceptor reflex.

A similar phenomenon has been recorded clinically by Anderson et al, who found that patients suffering moderate injuries, such as long bone fractures, showed a reduction in baroreflex receptor sensitivity within a few hours of their injury. The reflex had not returned to its normal sensitivity even after 14 days. Driscoll also suggested that there was a reduction in baroreflex sensitivity and a right shift in baroreflex setting in patients with significant tissue injury in addition to blood loss. Figure 2 also shows that, in those animals subjected to hind-limb ischaemia, there is no bradycardia as haemorrhage progresses. Such a bradycardia is normally mediated by the ‘depressor’ reflex and an increased vagal tone to the heart. Thus, tissue injury also seems to interfere with this reflex pathway.

It is clear that the cardiovascular responses to haemorrhage and tissue injury are quite different. However, central integration of the various reflex pathways is such that the cardiovascular response, when the two conditions occur simultaneously, resembles the response to tissue injury more than haemorrhage.

![Fig. 2 Cardiovascular response to haemorrhage and hind-limb ischaemia. The figure shows the effects of progressive haemorrhage (Haem), and the effects of haemorrhage in the presence of bilateral hind-limb ischaemia (H+LI), on heart rate (HR), in the upper panel, and mean arterial blood pressure (MAP), in the lower panel, in the conscious rat. Values are expressed as means ± SE. Adapted from Kirkman et al.](image)
Systemic responses to trauma

Consequences of haemorrhage and tissue injury: oxygen transport

The cardiovascular responses are accompanied by important changes in oxygen transport. Rady et al. found that, in the anaesthetised pig, oxygen delivery (DO₂I) was halved by a 40% TBV haemorrhage while oxygen consumption (VO₂I) was maintained. This was achieved by an increase in oxygen extraction ratio (OER) from 30% to 67% and a fall in mixed venous oxygen saturation (SvO₂) from 72% to 34%. When haemorrhage occurred on a background of somatic afferent nerve stimulation (SANS - to mimic tissue injury) DO₂I was reduced to 27%. At the same time, VO₂I fell to 53% despite an increase in OER from 37% to 81% and a fall in SvO₂ from 66% to 20%. Somatic afferent nerve stimulation itself was found to have no effect on either DO₂I or VO₂I, although it did produce the expected pressor response to tissue injury (tachycardia, increase in arterial blood pressure and increase in systemic vascular resistance).

A later study showed that skeletal muscle injury (SMI) had a qualitatively similar detrimental effect. The precise mechanism for the deleterious effects of SANS and SMI are not clear. It may be that SANS or tissue injury causes an increase in critical oxygen delivery (the level of DO₂ below which VO₂ becomes supply-dependent) as has been demonstrated by Kirkman et al., which, in turn, may be dependent on the redistribution of blood flow away from certain metabolically active organs, such as the gut, towards more inactive skeletal muscle.

Consequences of haemorrhage and tissue injury: regional blood flows

It was apparent that, in the initial phase of haemorrhage, there was an increase in systemic vascular resistance (SVR), which helped maintain arterial blood pressure in the face of a fall in cardiac output. Fore-arm blood flow was unchanged, suggesting that the increase in SVR was caused by vasoconstriction in other vascular beds.

Vatner found that, in conscious dogs, mild haemorrhage (resulting in a tachycardia but no fall in blood pressure) resulted in increases in mesenteric and iliac vascular resistance, but a reduction in renal vascular resistance. With moderate hypotensive haemorrhage, there was a greater reduction in mesenteric blood flow than in coronary blood flow, suggesting redistribution of flow in favour of the heart at the expense of other internal organs.

When haemorrhage or hypovolaemia is taken further so that there is profound hypotension, regional blood flows may alter again. Barcroft et al. found that when their volunteers became hypotensive and fainted, there was a sudden fall in SVR and a sudden increase in fore-arm blood
flow, suggesting a sudden skeletal muscle vasodilatation. A similar skeletal muscle vasodilatation occurred when sheep were haemorrhaged until an abrupt fall in blood pressure was seen.

Regional vascular responses have also been studied using lower body negative pressure (LBNP), in volunteers, to simulate hypovolaemia. The first study showed that splanchnic blood flow was more sensitive to simulated hypovolaemia than renal blood flow, while the second showed that splanchnic blood flow remained depressed until the end of the study period 60 min after reversal of LBNP.

Another indication of the vulnerability of gut blood flow came from an examination of microvascular blood flow following haemorrhage. Rats haemorrhaged to a MAP of 40 mmHg showed reductions in microvascular blood flow in the liver, spleen, kidney, small intestine and skeletal muscle, with the greatest reductions being seen in the small intestine and the kidney. Volume replacement with Ringer's lactate solution could only partially restore microvascular blood flow, which continued to deteriorate in all organs, even after resuscitation.

Parallels have been drawn between the responses to injury and the defence reaction. The essential components of the regional vascular changes during the 'defence reaction' are an increase in splanchnic vasoconstrictor tone and a reduction in vasoconstrictor tone to skeletal muscle, thus preparing the organism for 'fight or flight'.

When haemorrhage, in a pig model, occurred on a background of somatic afferent nerve stimulation (SANS, to mimic tissue injury) there was an alteration in the pattern of vascular response. In haemorrhage alone (30% of TBV), vascular resistance in the femoral bed more than doubled, while resistance in the splanchnic bed hardly changed. When 30% TBV haemorrhage was superimposed on SANS, there was a much smaller increase in femoral resistance. Splanchnic resistance increased, showing that with the additional insult of SANS (mimicking tissue injury), there was a relative diversion of blood away from the gut towards skeletal muscle (Fig. 3).

**Consequences of haemorrhage and tissue injury: gut mucosa**

Do the changes in gut blood flow, which are seen with both simple haemorrhage and haemorrhage with tissue injury have any major functional consequences? There now appears to be ample evidence that reduced gut blood flow, or haemorrhagic shock, can result in mucosal ischaemia and eventually to mucosal damage. The gut mucosa plays an important role as a barrier between the host and the gut microflora, which contains potential pathogens and toxins. Even in resting conditions the gut mucosa appears hypoxic compared to the serosa. Gut mucosal
Fig. 3 Changes in regional vascular resistances in response to haemorrhage and somatic afferent nerve stimulation. The figure shows the changes in femoral vascular resistance (upper panel), and gut vascular resistance (lower panel) before and after a 30% TBV haemorrhage (Haem), and after the same haemorrhage in the presence of brachial nerve stimulation (HNS). Values are expressed as means ± SE. Adapted from Mackway-Jones et al. 33

Oxygen tension \( (\text{PmO}_2) \) was found to be very sensitive to changes in blood volume: there was a fall in \( \text{PmO}_2 \) before any change in MAP or serosal oxygen tension \( (\text{PsO}_2) \). By the time blood loss reached 15%, \( \text{PmO}_2 \) had fallen by 40% with minimal changes in MAP and \( \text{PsO}_2 \). This provides further evidence for potential hypoxia of the gut mucosa in the face of haemorrhage.

Any ischaemic insult to the mucosa may result in a loss of this barrier function and the translocation of organisms or toxins from the gut lumen into the host lymphatics or circulation.

Consequences of haemorrhage and injury: translocation of bacteria and endotoxin

As early as 1952, the suggestion was made that ‘tissue anoxia of shock might stimulate invasion of the liver by intestinal flora’. It was not until the 1970s that the term translocation was applied to the movement of organisms from the gut lumen into either the systemic circulation, the lymphatics, or the peritoneum. By the late 1980s, the gut had been heavily implicated in the development of multiple organ failure (MOF). 40,41

Bacterial translocation is well documented in rodents, in which enteric organisms have been cultured after haemorrhagic shock. 42-46. Feeding rats \([^{14}\text{C}]-\text{labelled Escherichia coli} \) showed that the organisms originated in the gut. 47.
In large mammals, the evidence is mixed but a number of investigators have demonstrated translocation in swine\textsuperscript{48,49}, sheep\textsuperscript{50,51}, and baboons\textsuperscript{52}. Other investigators found no evidence of translocation in swine\textsuperscript{53,54}. A direct link between gut blood flow and bacterial translocation has been shown in pigs subjected to a 40\% BSA burn\textsuperscript{55}.

Translocation in humans remains controversial. Moore \textit{et al} inserted portal vein catheters in 20 trauma patients undergoing emergency laparotomy to take serial portal venous blood samples\textsuperscript{56}. Endotoxin assays performed over the first 48 h were negative. Although 30\% of these patients went on to develop MOF, the investigators found no evidence that MOF was caused by gut-derived organisms. In another study, no evidence of bacterial translocation from mesenteric lymph nodes, excised at laparotomy, was found in 25 blunt trauma patients, despite the fact that 28\% suffered major infectious complications with enteric pathogens\textsuperscript{57}.

In contrast, two studies, which used immunofluorescence to look for evidence of the breakdown products of translocated organisms in mesenteric lymph nodes of trauma patients, both gave positive results\textsuperscript{58,59}. Positive blood cultures were found in 13 of 50 trauma patients very shortly after their injury. The incidence of positive cultures was related to blood pressure on admission. For 10 of these, the average admission blood pressure was 45 mmHg. Whether these patients provide evidence for bacterial translocation as part of the pathophysiology of trauma is debatable: bacterial translocation may simply have been an agonal event\textsuperscript{60}.

If endotoxaemia is taken as an index of translocation, then it has been shown to occur on the day of injury and to increase until day four in burns patients\textsuperscript{61}. No endotoxaemia was found in two series of trauma patients\textsuperscript{56,62}, while only 7\% of patients in haemorrhagic shock had raised endotoxin concentrations\textsuperscript{63}.

There can be little doubt that bacterial translocation occurs in rodents. From the evidence in man one may suggest that finding live organisms in the circulation or the reticulo-endothelial system is a rare, possibly agonal, event. Immunofluorescence and microscopy have suggested that organisms may translocate across the gut mucosal barrier but that they are then killed by the secondary defences.

**Immunological consequences of trauma**

Late deaths from trauma continue to be a problem\textsuperscript{6,7,64}. Most of these are the result of MOF. This late development of a systemic illness is not a new phenomenon: after the battle of El Alamein, a surgeon wrote that\textsuperscript{65}: 'severe wounding was often followed by an illness, more or less serious and lasting at least several days, in which many factors other
than blood-loss or its late effects operated'. The precise nature of the 'many factors' has been a source of debate ever since. The evolution of this debate was summarised in 1996.

It is clear that the immune system is intimately involved in the response to trauma. The production of various cytokines after trauma will be used to illustrate this. It would be impossible to review all aspects of the immune response to trauma in such a short review. Two books will provide a very valuable introduction to this field.

Consequences of haemorrhage and tissue injury: cytokine production

Inflammatory response

Inflammatory cytokine production has been described in models of haemorrhagic and traumatic shock. Ayala et al have suggested, as a result of their studies with rodent models of haemorrhage and tissue injury, that the two insults act as slightly different triggers for cytokine production. It seemed that tumour necrosis factor α (TNFα) was only produced after haemorrhage, but that interleukin-6 (IL-6) production could be stimulated by tissue injury before any haemorrhage.

It is clear from a number of studies of elective surgery that the tissue injury caused by surgery will stimulate the production of interleukin-1 (IL-1), and/or IL-6. Indeed, it appears that the production of IL-6 is linked to the severity of the tissue injury inflicted. In these studies, IL-6 production was detectable within 2 h of the initial incision and the peak was seen within a few hours, unlike the peak in C-reactive protein, which tended to occur the following day.

Deitch et al suggested that the gut acted as a cytokine-producing organ since levels of TNFα and IL-6 were higher in portal venous blood than in systemic blood.

Thus, it appears that the vascular responses to haemorrhagic and traumatic shock can result in functionally important reductions in gut blood flow so that there is a breakdown of the gut mucosal barrier. Once this has happened, bacterial or endotoxin translocation may occur with potential triggering of the production of inflammatory mediators, such as cytokines. This may represent the initiation of a chain of events leading to a process of systemic inflammation which may ultimately produce multiple organ failure.

Clinical studies

Studies of elective surgery have shown that there seems to be some correlation between the degree of tissue injury and the production of IL-6. This has been confirmed in several trauma series, and in burns.
Raised inflammatory cytokine concentrations were found on the day of admission, after trauma, and then gradually declined over the next 48 h in patients making a good recovery\(^62,81\). However, there was good evidence for a secondary increase in cytokine production, later, in those patients developing septic complications\(^62,81-83\). Initial cytokine concentrations were not predictive for those patients who would develop septic complications.

The role of TNF\(\alpha\) in the cytokine response to trauma remains very unclear. Many studies have found that TNF\(\alpha\) was either undetectable, or only detectable in a minority of patients after trauma\(^62,81,84-87\).

It has been suggested that the TNF\(\alpha\) response is too transient to be detected in most studies. A study using blood taken at the scene of the accident concluded that TNF\(\alpha\) was active in the inflammatory response due to trauma and that it might be activated early and may have modulated subsequent cytokine activity\(^88\).

Raised plasma TNF\(\alpha\) concentrations have been found in haemorrhagic shock patients\(^63\). There was no correlation between TNF\(\alpha\) concentrations and the degree of haemorrhage (as assessed by the volume of blood transfusion), nor was there a difference in TNF\(\alpha\) concentrations between those patients developing MOF and those who did not. However, most studies have shown that TNF\(\alpha\) concentrations are higher in those patients who do become septic after trauma, than in those who do not\(^62,81-83,89\).

**Anti-inflammatory responses**

Trauma not only results in the production of various inflammatory cytokines. Interleukin-10 (IL-10) has been characterised as an anti-inflammatory cytokine\(^90-93\), and its production has been measured in trauma patients\(^94\). Plasma IL-10 was associated with hypotension on admission, and the development of sepsis, but was not related to the severity of injury. In contrast, in another study, higher IL-10 concentrations were seen in patients with an ISS greater than 25 than in those with a lower ISS\(^95\). In this same group of 401 patients, higher IL-10 concentrations were measured in those patients who became septic and those who developed multiple organ dysfunction syndrome (MODS). The authors suggested that IL-10 might actually be involved in the pathogenesis of sepsis and MODS after injury. This seems to run counter to the ideas generated by laboratory studies.

Other endogenous anti-inflammatory mediators have been examined. There is good laboratory evidence for a protective effect of the endogenous inhibitor of IL-1, interleukin-1 receptor antagonist (IL-1ra), in endotoxaemia\(^96,97\). Elective surgery has been shown to result in an increase in IL-1 inhibitory activity over a 24 h period, but there was still
an increase in IL-6 and in the C-reactive protein, mostly after IL-1 inhibitory activity had returned to baseline\textsuperscript{75}. An increase in IL-1ra was seen in 22 trauma patients, but the concentration of IL-1ra and other soluble cytokine receptors, was higher in non-survivors than in survivors\textsuperscript{98}. The authors suggested that these receptors might be markers of the severity of the insult, rather than contributors to the mortality. Although inflammatory cytokines were undetectable, it does not appear that the anti-inflammatory mechanisms had a very protective function.

Soluble TNF receptors (sTNF-Rs) are produced in trauma patients\textsuperscript{98,99}, but, in both studies, concentrations were higher in non-survivors than in survivors. If they had a protective anti-inflammatory function one might expect that the non-survivors would be those patients unable to produce the receptors, rather than those who produced the most. Interestingly, sTNF-R concentrations decreased during episodes of infection or hypoxia in individual patients\textsuperscript{99}. Maybe these reductions in sTNF-R concentrations do indicate a loss of endogenous anti-inflammatory activity during secondary episodes of sepsis. This may form part of the basis of the ‘two-hit’ model for the development of MOF.

**Activation of cytokine production**

Bacterial and/or endotoxin translocation from the gastrointestinal tract has been advanced as one possible mechanism for the activation of cytokine production. Deitch et al have suggested that, even in the absence of live translocating organisms or endotoxin in the portal and systemic circulations, the gut can still act as a cytokine generator via the activation of the gut associated lymphoid tissue\textsuperscript{71}.

Alternatively, it could be that cytokine production is triggered directly at the wound site. Evidence for this comes from both a rat model and a clinical situation\textsuperscript{100}. Raised levels of IL-6 were found in both wound fluid and serum of rats subjected to polyvinyl alcohol sponge implantation, and in fluid draining from mastectomy scars. This suggested that cytokines found in the systemic circulation might have originated at the wound site. Both IL-1 and IL-6 were found in the blisters of burned children, although IL-1 was generally absent from the circulation, again suggesting local production\textsuperscript{101}.

It may be that two mechanisms act together or act independently on different cytokines: IL-6 being triggered to a greater extent at the wound site by tissue trauma while TNFα and IL-1 might be more sensitive to changes in gut barrier function and activation of the gut associated lymphoid tissue.

The question remains as to the exact trigger mechanism for the cytokine production seen in trauma and burns patients. The macrophage hypothesis of activated macrophages producing cytokines and
other mediators which then result in systemic inflammation leaves the question of what activates the macrophages unanswered\textsuperscript{102}.

**Models for the development of post-trauma multiple organ failure**

A better understanding of the inflammatory responses after trauma has resulted in interesting models for the development of MOF. Moore \textit{et al} have divided the inflammatory response into two phases: an initial hyperinflammatory response (the systemic inflammatory response syndrome – SIRS), followed by a phase of immunosuppression\textsuperscript{103,104}. This model was a response to several studies\textsuperscript{104,105}, which showed that there were two types of MOF patients: those who went into MOF ‘early’, and those who went into MOF ‘late’.

The other model is that of the ‘one-hit’ or ‘two-hit’ insult resulting in early MOF\textsuperscript{103,106}. In this model, patients may go into MOF, either because of one early and massive traumatic insult, which causes so much inflammation that MOF ensues, or, if the initial insult is not massive, then this inflammatory response may be triggered by a secondary insult such as definitive surgery a few days after the trauma. Secondary surgery has been reported as a trigger for MOF\textsuperscript{107}. The validity of these ideas has aroused some controversy\textsuperscript{108,109}. Even if there is debate about this model it does serve as a warning that there may be a risk to delaying definitive surgery for orthopaedic injuries, for example. There may be an argument for either doing early “damage control surgery” or delaying for a week or more, until after the worst of the hyperinflammation\textsuperscript{110,111}.

**Summary**

In this review, I have tried to show that trauma elicits a variety of cardiovascular responses. The responses to haemorrhage and to tissue injury are different and the two insults interact to produce changes in organ blood flow and oxygen delivery. These changes may have important effects on the gut and gut mucosal integrity. The gut has been heavily implicated in the development of MOF\textsuperscript{40,41}.

Whether or not the gut and bacterial translocation are relevant in man, it is now clear that there is an inflammatory response after trauma. The development of that response seems to be responsible for the development of MOF, either by a ‘one-hit’ or by a ‘two-hit’ process in the early stages, or later as the result of immunosuppression.

By understanding these responses, attempts can be made to optimise the resuscitation and later care of trauma patients. As a recent review
stated: ‘patients in shock, if they are to survive the initial insult, are still at risk of dying on a subacute basis from continuing global hypoperfusion and the resultant multiple organ dysfunction, if they are inadequately resuscitated...It is clear that adequate resuscitation goes beyond the restoration of a normal blood pressure and urine output.’

References

3. Trunkey DD. Trauma. Sci Am 1983; 249: 20-7
8. Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer EP. Posthaemorrhagic fainting study by cardiac output and forearm flow. Lancet 1944; i 489-91


51 Navaratnam RLM, Morris SE, Traber DL et al. Endotoxin (LPS) increases mesenteric vascular resistance (MVR) and bacterial translocation (BT) J Trauma 1990; 30: 1104–15


54 Foex BA. The haemodynamic response to haemorrhage and injury, and its consequences in the anaesthetised pig. North Western Injury Research Centre. Manchester: Manchester, 1998; 398


61 Winchurch RA, Thupari JN, Munster AM. Endotoxemia in burn patients: levels of circulating endotoxins are related to burn size. Surgery 1987; 102: 808–12


65 Wilson W. State of men severely wounded in battle. Lancet 1944; i: 587–91


69 Ayala A, Perrin MM, Meldrum DR, Ertel W, Chaudry IH. Hemorrhage induces an increase in serum TNF which is not associated with elevated levels of endotoxin. Cytokine 1990; 2: 170–4


84 Foex BA, Lamb WR, Roberts TE et al. Early cytokine response to multiple injury. Injury 1993; 24: 373-6


89 Endo S, Inada K, Inoue Y et al. Two types of septic shock classified by the plasma levels of cytokines and endotoxin. Circ Shock 1992; 38: 264-74


91 Marie C, Pitton C, Fitting C, Cavaillon JM. Regulation by anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGFbeta) of interleukin-8 production by LPS- and/or TNFalpha-activated human polymorphonuclear cells. Mediators Inflamm 1996; 5: 334-40

92 Marie C, Cavaillon JM. Le retrocontrole negatif de l'inflammation: role des cytokines antinflammatoires Bull Inst Pasteur 1997; 95: 41-54


95 Neidhardt R, Keel M, Stendahler U et al. Interleukin-10 (IL-10) plasma levels from injured patients correlate with severity of injury and clinical outcome. 56th Annual Meeting of the American Association for the Surgery of Trauma. Houston, Texas: American Association for the Surgery of Trauma, 1996; 424


97 Fischer E, Marano M, Van Zee K et al. Interleukin-1 receptor blockade improves survival and hemodynamic performance in Escherichia coli septic shock, but fails to alter host response to sublethal endotoxemia. J Clin Invest 1992; 89: 1551-7

98 Cinat M, Waxman K, Vazin N et al. Soluble cytokine receptors and receptor antagonists are sequentially released after trauma. J Trauma 1995; 39: 112-20


100 Mateo RB, Reichner JS, Albina JE. Interleukin-6 activity in wounds. Am J Physiol 1994; 266: R1840-4