Multiple organ failure is a common mode of death following abdominal aortic aneurysm repair, particularly after rupture. Cytokines are the principal mediators of the inflammatory response to injury and high levels of circulating cytokines have been associated with poor outcome in major trauma and sepsis. Abdominal aortic aneurysm repair results in an ischaemia-reperfusion injury to the tissues distal to the site of aortic clamping. The inflammatory response in these tissues causes the release of cytokines, principally Interleukins 1-beta, 6, and 8, and Tumour Necrosis Factor alpha. If released in large enough concentrations, these cytokines may enter the circulation and gain access to organs distant to the site of initial injury. Circulating cytokines cause dysfunction of the renal, cardiovascular, respiratory, nervous and musculo-skeletal systems. The combination of these individual changes in organ function is the multiple-organ dysfunction syndrome, which may progress to multiple organ failure.

Key Words: Aortic aneurysm; Abdominal; Cytokines; Multiple organ failure; Critical care.

Introduction

Death following repair of ruptured abdominal aortic aneurysms (AAA) is usually due to multiple organ failure. Ischaemia-reperfusion injury following aortic cross-clamping leads to activation of inflammatory pathways, resulting in injury to distant organs such as the lungs and kidneys which may initially dysfunction and eventually fail.

Multi-organ dysfunction syndrome (MODS) was originally described in association with infective insults but a similar syndrome is seen in patients with no infective focus such as trauma victims and those recovering from major surgery. This has been termed the systemic inflammatory response syndrome (SIRS) and the widespread activation of inflammatory cascades has been implicated in its genesis. Cytokines are the major mediators of this response and exert local and distant effects. SIRS is often seen in patients following AAA repair and increased levels of circulating cytokines have been observed in these patients.

This paper reviews the role of cytokines in the pathophysiology of MODS following AAA repair with particular reference to how individual organs injured by AAA repair contribute to the overall inflammatory response to surgery and how circulating cytokines cause dysfunction of major organ systems.

Methods

A systematic search of the Medline (1966 to December 2000) and Embase (1980 to December 2000) electronic databases were performed by one of the authors (MJB). The Ovid search engine (version 7.8) was employed. Searches based on the intersection of the MeSH keyword cytokine with the following keywords were examined: aortic aneurysm, abdominal; multiple organ failure; reperfusion injury; brain; lung; heart; liver; renal; “gastrointestinal system”; “musculoskeletal system”. In addition, manual searching of reference lists from articles retrieved by electronic searching was used to identify articles missed by the electronic searches. Articles retrieved were restricted to those published in English. Articles were selected for inclusion if they concerned the production of cytokines...
by tissues subjected to ischaemia-reperfusion injury by AAA repair or if they gave details of the effect of circulating cytokines on any organ system.

**The injury of AAA repair**

Aortic cross clamping is the significant insult during AAA repair. The incidence of major complications and death following AAA repair is much greater than for other common procedures requiring a laparotomy for surgical access such as a bowel resection. Although retroperitoneal AAA repair is associated with a shorter ITU stay and a reduced degree of post-operative ileus, the mortality and morbidity is similar to that following transperitoneal AAA repair. Aortic cross clamping causes ischaemia-reperfusion injury and widespread activation of inflammatory pathways. For patients with ruptured aortic aneurysm there are the additional insults of haemorrhage, acidosis and blood transfusion. This so called “second hit” phenomenon causes further activation of inflammatory pathways. Complications following AAA repair often occur in organs distant to the site of direct injury caused by aortic clamping. This distant organ injury has been shown to be neutrophil dependant, however it appears to be due to the activation of resident neutrophils in these organs rather than the influx of neutrophils from the site of injury. This activation of resident neutrophils must therefore be due to factors generated at the site of surgical injury passing in the circulation to these distant organs.

### Multi-organ failure and SIRS

Multi-organ failure (MOF) was first described in patients who had undergone emergency repair of a ruptured AAA and is associated with a high mortality. The mortality following failure of a single organ system is around 30% and each additional organ system failure increases the risk of death in a multiplicative fashion. The sequential failure of organ systems over time is the defining characteristic of MOF. MOF is the most common cause of death in patients on ITU and frequently presents with a syndrome resembling sepsis: pyrexia, leucocytosis, dyspnoea and a hyperdynamic circulation. For this reason early studies of MOF focused on infection as the underlying cause. However, MOF was also noted following major trauma where no infective aetiology could be implicated and further studies revealed that the presentation of MOF in patients with infective insults was similar to that in victims of trauma. This led to the theory that MOF is a result of an inflammatory/immunological response to the initial insult rather than the nature of the insult itself.

In order to identify those patients in whom these inflammatory responses have become activated and are at risk of developing MOF, the systemic inflammatory response syndrome (SIRS) has been defined (Table 1). During the progression from SIRS to MOF a patient may have not developed complete organ failure but individual organ systems may be functioning abnormally. Multiple organ dysfunction syndrome (MODS) has been defined as the detection of altered organ function in the acutely ill patient such that homeostasis cannot be maintained.

### Cytokines

Cytokines are low molecular weight glycoproteins that were first identified as being produced by cells of the immune system and involved in the regulation of immune system responses and intercellular signalling. Recently other cell types such as fibroblasts, smooth muscle cells and endothelial cells have been recognised as capable of cytokine production. Circulating cytokines are an integral part of the inflammatory and immune responses. Absolute amounts of cytokine production are usually very low (picomolar concentrations) and this limits their actions to the local tissues. The excessive production of cytokines and overspill into the systemic circulation is responsible for their role in SIRS and MODS. This effect was originally demonstrated in animal models whereby injection of TNF-α induced a syndrome clinically identical to shock.
Table 2. Cytokines identified during critical illness and clinical significance.

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Cytokines identified</th>
<th>Significant outcome associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial sepsis^22-30^</td>
<td>IL-10, TNF-α, IL-6,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-12, TNF-sR</td>
<td>Elevated IL-6, TNF-sR associated with non-survival</td>
</tr>
<tr>
<td>Intra-abdominal sepsis^41^</td>
<td>IL-6, TNF-sR, IL-1Ra</td>
<td>Elevated IL-6 associated with non-survival</td>
</tr>
<tr>
<td>Severe sepsis/septic shock in a surgical</td>
<td>TNF-α, IL-6, IL-8</td>
<td>TNF-α, IL-6 and IL-8 levels higher in septic shock than severe sepsis</td>
</tr>
<tr>
<td>intensive care unit^41^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major trauma^42,43^</td>
<td>IL-10</td>
<td>Elevated IL-10 associated with incidence of sepsis/MODS</td>
</tr>
<tr>
<td>Sepsis syndrome^44^</td>
<td>TNF-α, IL-1β, IL-6</td>
<td>Elevated IL-6 associated with non-survival</td>
</tr>
</tbody>
</table>

The production of cytokines by cells of the inflammatory and immune systems is triggered during activation of the inflammatory cascades. Cytokines can be broadly divided into those with primarily pro-inflammatory actions and those with anti-inflammatory actions. Pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α promote the further liberation of cytokines and cause the classical signs of inflammation.

The actions of pro-inflammatory cytokines are necessarily limited by auto-regulatory mechanisms. Principal among these are the anti-inflammatory cytokines and the very short half-lives of cytokines limiting their duration of action. IL-10 is a potent anti-inflammatory cytokine. It inhibits macrophage function^32^ and acts indirectly on T-cells by interfering with the antigen presenting cell signals to the T-cells.^33^ It reduces pro-inflammatory cytokine production by macrophages, neutrophils and T-cells. Naturally occurring antagonists to some cytokines have also been identified. These can be soluble receptors (TNF-sR)^34^ or structurally related peptides with no apparent action (IL-1 receptor antagonist – IL-1Ra).^35^

Whilst TNF-α is the prototypical mediator of sepsis the identification and study of other inflammatory/immune system mediators has revealed complex interactions between these mediators. The examination of individual cytokines is largely academic. All cytokines act as part of a network, the balance of pro- versus anti-inflammatory mediators defines the overall response. RC Bone describes this balance in terms of SIRS and the concept of a compensatory anti-inflammatory response syndrome (CARS).^36^ Predominance of SIRS (pro-inflammatory pathways) leads to shock, apoptosis and organ dysfunction whilst excessive activation of CARS (anti-inflammatory pathways) results in immune system depression.

Most cytokines are not normally detectable in healthy individuals but during critical illness elevated levels of cytokines have been identified in many studies (Table 2).

The clinical importance of elevated cytokine levels during sepsis has, in some cases, been examined. Non-survival has been associated with high levels of IL-6, TNF-sR, IL-8 and IL-10 (see Table 2). High levels of pro-inflammatory cytokines represent excess activation of the inflammatory system and SIRS. Raised IL-10 is probably associated with mortality through its immunosuppressive effects. ^45^ Roumen et al.^5^ examined TNF-α, IL-1β and IL-6 following AAA repair. High immediate post surgery levels of both IL-1β and TNF-α, and IL-1β levels at 24 hours were significantly associated with increased mortality. High levels of IL-6 correlated with the presence of adult respiratory distress syndrome (ARDS) and a high MOF score. Holmberg et al.^4^ measured IL-6, IL-10, MCP-1 and soluble IL-2 receptor (sIL-2R) during and one week after aneurysm surgery; all were significantly elevated, with the greatest increase immediately after aortic declamping. The recent systematic review by Swartbolin et al.^46^ gives a complete summary of these and other studies examining cytokine responses to AAA repair.

The Generation of Cytokine Responses to AAA Repair

Aortic clamping causes an ischaemia-reperfusion (IR) injury in tissues distal to the site of the clamp. The IR injury in distal tissues leads to cytokine release and subsequently the clinical effects of SIRS and possibly MOF.

Distal vasculature

Endothelium damaged by IR produces complement, arachidonic acid metabolites such as prostaglandin E2 and thromboxane A2 and up-regulates adhesion molecule expression (ICAM 1 and 2, VCAM 1).^47^ Neutrophils bind to adhesion molecules via integrins and become activated. These activated neutrophils migrate across the endothelium and cause further local
tissue damage by releasing lysosomal contents and free radicals. Reduced nitric oxide (NO) production in endothelium following IR impairs endothelial function and in turn vascular homeostasis. These processes cause cytokine release via activation of neutrophils and direct production of cytokines by the endothelial and vascular smooth muscle cells themselves. Hypoxia, independent of reperfusion has been shown to induce IL-6 production by endothelial cells.49

Lower limbs

The cytokine profiles seen following isolated limb IR in humans have not been studied in detail. Raised IL-1 and TNF-α have been observed following tourniquet-induced limb ischaemia.48 IL-6, IL-10 and IL-1Ra have also been observed following traumatic and tourniquet-induced limb ischaemia, however the effects of trauma in these patients may confound the true response due to IR alone. In animals skeletal muscle IR results in the production of TNF-α and IL-1.53 Whether this is quantitatively significant in patients undergoing AAA repair is unclear. Holmberg et al.6 found no difference in IL-6 and IL-10 levels between femoral and cubital venous samples taken immediately after aortic de-clamping during AAA repair.

Gastro-intestinal tract

In ruptured AAA haemorrhagic shock causes splanchnic vasoconstriction which leads to intestinal hypoperfusion and ischaemia. Upon resuscitation the gut is reperfused and an IR injury is sustained. This has been implicated in the generation of MODS. Loss of gut barrier function occurs following intestinal IR and consists of increased mucosal permeability (via NO, locally acting cytokines (IL-13, IL-4, Platelet-Activating-Factor (PAF)) and superoxide mechanisms) and bacterial translocation.60 Bacterial translocation causes localised inflammation and consequently further cytokine production. Bacterial translocation also allows bacteria and endotoxin normally contained within the gut lumen to enter the portal and systemic circulations. Elevated systemic TNF-α and portal endotoxaemia have been demonstrated in animal models of intestinal IR.61,62 Kupffer cells in the hepatic sinusoids are exposed to these and activated. Activated Kupffer cells release cytokines, particularly TNF-α, into the circulation.63 Treatment with IL-10 reduces systemic TNF-α and IL-6 following intestinal IR and IL-6 knockout mice show reduced systemic levels of TNF-α and IL-1β in response to intestinal IR.65 This demonstrates the pro- and anti-inflammatory effects of IL-6 and IL-10 respectively.

Elevated levels of TNF-α in the portal circulation have been observed following elective AAA repair.66 The reasons for this are not clear. Animal studies have demonstrated increased intestinal permeability after isolated hind-limb ischaemia, suggesting that this is mediated via factors generated in the tissues subjected to injury which in turn exert their effects on the gastrointestinal tract.67 In humans elective aortic surgery is associated with increased intestinal permeability despite no direct IR injury to the gut and this may be caused by a similar mechanism or it may be due to cooling and handling of the gut during repair.68

During elective AAA repair an IR injury may be sustained by the distal large bowel if it’s circulation is dependant on the internal iliac system. Using intramucosal sigmoid pH monitoring Soong et al. demonstrated that during elective AAA repair low sigmoid pH, indicating ischaemia, was not dependant on any intra-operative factors and also that low pH was associated with higher post-operative endotoxin, TNF-α and IL-6 concentrations.69 Higher levels of portal endotoxaemia and larger increases in intestinal permeability have been observed in patients undergoing transperitoneal AAA repair compared to retroperitoneal repair and this has been attributed to manipulation of the bowel during transperitoneal repair.70

Kidneys

During the majority of elective AAA repairs supra-renal cross-clamping of the aorta is avoided. However infra renal clamping also causes renal damage and changes in renal perfusion. Supra-renal aortic clamping is more frequently employed during emergency surgery due to the need to gain rapid control of haemorrhage. This, in addition to the insult of significant haemorrhage results in a higher mortality due to acute renal failure post-operatively.71 The cessation or re-distribution of renal blood flow produces a total or partial ischaemic insult to the renal parenchyma. Upon reperfusion the ischaemic tissue sustains an IR injury. Animal studies have demonstrated elevated tissue levels of IL-1, IL-2, IL-6, TNF-α, TGF-β and IFN-γ after renal IR.72,73

The cytokine profiles generated by patients undergoing AAA repair are the sum of those produced by
the above organ injuries. The proportion that each organ contributes to the total is not clear.

In summary, aortic cross-clamping causes an ischaemia-reperfusion injury to distal tissues. As shown above this injury generates cytokines in these tissues. If produced in large enough quantities, they may enter the systemic circulation and if regulatory mechanisms are overwhelmed, they gain access to distant organs. The effects of cytokines on the function of these organ systems are described below.

**Cytokine Effects in Distant Organ Systems**

**Vasculature**

Cardiovascular instability and in particular the loss of normal endothelial function are prominent features of MODS. Neutrophil-endothelial interactions significantly contribute to the effects seen in distant organs following IR. Cytokines have profound effects on vascular tone, largely mediated via changes in the nitric oxide (NO) pathway. As blood pressure is directly related to systemic vascular resistance a drop in vascular tone results in decreased blood pressure and reduced organ perfusion.

NO is produced by nitric oxide synthase (NOS) and is the direct mediator of vasodilatation. In keeping with their pleiotropic nature different cytokines can have different effects on NOS. The initial studies on TNF-α as a mediator of septic shock demonstrated that its administration produced systemic hypotension and other signs of septic shock although the mechanisms of this response were not known. Similar responses to IL-1β have been observed and also the failure of response to vasoconstrictors following prolonged exposure to these cytokines. These two cytokines (TNF-α, IL-1β) have been shown to increase NO production and also promote the production of inducible NOS (iNOS) by both endothelial and vascular smooth muscle cells. Alongside the increase in iNOS expression, constitutively produced endothelial NOS (eNOS) expression is inhibited via decreased eNOS mRNA stability. This leads to a change in the site of NO production from endothelial cells to smooth muscle cells. This change in site of NO production may facilitate adhesion molecule expression as inhibition of cytokine-induced endothelial cell adhesion molecule expression by NO has been demonstrated.

In addition to affecting vascular function IL-1β and TNF-α also cause further cytokine release from endothelial and vascular smooth muscle cells. These include IL-6, chemokines and IL-1β. The effects of anti-inflammatory cytokines on the vasculature are not clear. IL-10 has been shown to increase IL-6 expression in mouse endothelial cells and potentiate the action of TNF-α and IL-1. This is contradictory to its general effects as an anti-inflammatory cytokine.

Adhesion molecules play an integral role in endothelium–leucocyte interactions. While the precise role of each different adhesion molecule is not clear, VCAM-1 and ICAM-1 have been shown to be necessary for leucocyte adhesion. Leucocyte adhesion to endothelium is increased in response to cytokines and this is due to cytokine mediated upregulation of adhesion molecule expression.

The anti-inflammatory effects of TGF-β are partially due to the inhibition of pro-inflammatory cytokine-stimulated endothelial VCAM-1 expression.

**Respiratory system**

The above changes in the microcirculation are necessary for neutrophil-endothelial adhesion and subsequent extravasation of neutrophils, an essential step in the normal inflammatory response. However, the tissue damage caused by widespread excessive neutrophil activation is one of the causes of organ dysfunction following AAA repair. Respiratory failure is commonly part of MODS. In patients suffering from adult respiratory distress syndrome (ARDS) both pro- and anti-inflammatory cytokines have been detected in broncho-alveolar lavage fluid. Circulating cytokines in the venous circulation pass through the pulmonary vasculature and activate both resident leucocytes and the pulmonary vascular endothelium. The pulmonary vasculature acts as a neutrophil pool in normal physiological states and following endothelial activation, there is an increased potential for neutrophil–endothelial interactions in the lungs compared with other vascular beds. Together with the large surface area of the pulmonary vascular endothelium this means that the pulmonary vasculature is a quantitatively significant site of neutrophil–endothelial interactions.

Inflammatory pulmonary injury is caused by activated neutrophils and macrophages which have migrated from the pulmonary vasculature into the interstitial and alveolar spaces. Activated neutrophils produce locally cytotoxic hypochlorous acid and oxygen free radicals. Macrophages secrete IL-8, IL-1 and TNF-α. Type II pneumocytes release IL-6, IL-8, G-CSF and MCP-1 in response to bradykinins produced by local inflammation and further IL-8 is produced by TNF-α stimulation of interstitial fibroblasts. IL-8 is a potent neutrophil and macrophage chemotactant and
thus promotes persistence of local inflammation. All of these responses lead to the accumulation of inflammatory infiltrates in the alveoli and interstitium. These are responsible for the decreases in gas exchange and increased work of breathing seen in ARDS.

Renal

Acute renal failure is commonly seen following emergency AAA repair, either as a part of MODS or in isolation. Hypotension and supra-renal aortic clamping cause direct injury due to ischaemia and pre-existing chronic renal impairment exacerbates this. Cytokines are known to mediate renal damage following the IR injury of transplantation. TNF-α has been shown to induce glomerular injury in animals without prior renal insult. In kidneys already damaged by hypoperfusion or IR, cytokines can exacerbate this injury. Glomerular cells respond to TNF-α and IL-1 by producing complement, arachidonic acid derivatives, nitric oxide and oxygen free radicals. Mesangial cells produce IL-1, IL-6 and IL-8 in response to stimulation by IL-1 and IL-8. All of these cause or increase local inflammation and further glomerular and tubular damage.

Cardiac

Cardiac function is often impaired in MODS, and patients may require pharmacological and fluid support to maintain adequate end-organ perfusion. Patients with AAAs are at higher risk of ischaemic heart disease than the general population by virtue of similar risk factors and pathogenetic mechanisms underlying both disease processes. Thus they are likely to have reduced cardiac reserve and are therefore at increased risk of cardiac complications following surgery. IL-2 and TNF-α have been shown to impair cardiac function acutely through NO pathways. Cytokines act on cardiac myocytes to increase iNOS expression, leading to higher local levels of NO. NO is thought to exert its local effects by influencing the responses of cardiac muscle to adrenergic and cholinergic stimulation. Cytokines (TNF-α, IL-1β, IL-2, IL-6, IFN-γ) may actually mediate cardiac dysfunction by direct actions on the myocytes, although the mechanisms underlying these actions are not clear.
AAA Repair, Cytokines and Multiple Organ Failure

cause injury to those tissues supplied by branches of
the aorta immediately proximal to the site of clamping.
In the case of ruptured AAA this is combined with
haemorrhagic shock and subsequent resuscitation.
Cytokines are produced by inflammatory cells re-
cruited to these sites of damage and also by damaged
native cells, most significantly endothelial cells.
Removing the initial stimulus may have little or no effect
if the regulatory mechanisms have been overwhelmed
by pro-inflammatory positive feedback loops. The
above demonstrates the processes involved at single
organ level but the clinical response is the combination
of these and exhibited by the patient as a whole
(Fig. 1).

Pulmonary inflammatory infiltrates increase work
of breathing and decrease gas exchange causing ta-
chypnoea and hypoxaemia with progression to ARDS
if severe. Decreased cardiac contractility and loss of
vascular tone results in hypotension and decreased
organ perfusion. Decreased organ perfusion causes
further injury. Renal damage caused by cytokine me-
diated inflammation together with poor perfusion de-
creases renal function leading to oliguria, uraemia
and raised serum creatinine. Hypothalamic activation
causes pyrexia and HPA axis activation. The individual
organ responses are inter-related and dysfunction in
one system has a negative effect on others, causing
a vicious circle of progressively deteriorating organ
function. These clinical signs are those of SIRS and, if
significant organ dysfunction is present, MODS.

Discussion

Cytokines have been shown to potentially play a sig-
nificant role in the mediation of distant organ damage
following AAA repair and the development of MODS
(see Fig. 1). There is a great deal of evidence for
the roles of TNF-α, IL-1 and IL-6 in particular. IL-6
correlates well to the degree of surgical injury and has
been demonstrated to be a useful prognostic indicator
after AAA repair. Although other cytokines have
not been studied in detail they may be of equal or
greater importance. Current therapeutic options in-
clude targeting the cytokines themselves and reducing
the degree of initial IR injury.

Theoretically, blocking the action of pro-inflam-
matory cytokines or administration of anti-in-
flammatory cytokines could limit the extent of organ
failure. Selecting single molecules, for example TNF-
α as therapeutic targets has largely failed to achieve
any clinical effect possibly due to the pleiotropic nature
of cytokines. Compounds that have antagonistic effects
to more than one cytokine have shown benefit in
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Differences in the inflammatory response to endovascular and open AAA repair have been demonstrated by many authors\(^1\) although the results between centres are inconsistent with regard to individual cytokines and the difference between open and endovascular repair. Since peri-operative morbidity and mortality rates are similar after endovascular and open repair,\(^2\) it may be that whilst the mechanism by which the inflammatory response is generated is different, the activation of the inflammatory cascades results in a similar clinical scenario in both groups of patients.

Attempts have been made to use cytokine levels to predict outcome in patients suffering from SIRS/sepsis syndrome.\(^3\)\(^4\) These and other studies have identified a wide range of cytokine responses in patients with similar injuries.\(^5\)\(^6\)\(^7\)\(^8\) These differences in cytokine production from one individual to another may be partly due to genetic causes. The presence of polymorphic sites in cytokine genes has been shown to affect cytokine mRNA expression for some cytokines.\(^9\)\(^10\)\(^11\) The clinical effects of these polymorphisms are unclear. The most studied polymorphism is a guanine to adenine single base substitution in the TNF-α promoter sequence.\(^12\) This has been observed in different studies on patients with the sepsis syndrome to have either no effect on mortality\(^13\)\(^14\) or a many-fold increase in mortality.\(^15\) Their roles in outcome following AAA repair \textit{per se} have not been studied but may provide a method to improve outcome prediction in these patients if a particular polymorphism is associated with poor outcome.

The current evidence presented above largely concentrates on the immediate responses to injury. Death due to MOF following AAA repair usually occurs several days after the initial insult. The cytokine profiles generated by these patients during this period are different from those exhibited immediately post-operatively.\(^16\) Whilst the immediate cytokine response is responsible for the generation of the clinical syndrome seen, its persistence may be under the influence of different mediators and the study of cytokine levels during this time period may identify possible new therapeutic targets.

Whilst cytokines clearly play a central role in the generation and maintenance of SIRS and MODS following AAA repair it must be remembered that they are a small part of a wide-ranging physiological response to surgery. As such, whilst therapeutic interventions aimed at modification of cytokine mediated responses may have a role in the management of critical illness they are likely to achieve best results if used in concert with traditional and other novel management strategies.


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Intestinal permeability is increased after major vascular surgery.


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