Recent surveys document an increasing incidence of community-acquired and nosocomial infections in the United States, with a significant proportion of these infections occurring in an increasingly aged population with underlying health problems. Among surgical patients, the stresses of operation or injury also increase the risks for infection and solid organ dysfunction across all population demographics. The present incidence of acquired infection approximating 2% to 3% is likely to continue to increase among nontrauma surgical patients.

THE STRESSED CLINICAL PHENOTYPE

The manifestation of systemic inflammatory response syndrome (SIRS) criteria is the common clinical phenotype of stressed surgical patients. Concerns have repeatedly been expressed that SIRS lacks sufficient specificity and prognostic value since the time the concept was originally proposed as a mechanistically based risk stratification system. The SIRS concept does retain value within surgical populations in which morbidity and mortality risks are correlated to the expression and duration of SIRS.

In essence, the SIRS phenotype reflects the presence of consequential systemic inflammation and suggests increasing risk for complications and an adverse outcome if the criteria are manifested over an extended period. The initial inflammatory stimulus for SIRS may arise from any number of etiologies, including “sterile” stresses, such as pancreatitis, or cross-sectional tissue injury resulting from involuntary injury or surgical

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interventions. These injuries incite autonomic nervous and neuroendocrine signals that induce limited SIRS criteria, such as leukocytosis\textsuperscript{10,11} and increased heart rate, but the simultaneous presence of three or more SIRS criteria is infrequent without overt activation of the innate immune system. It remains to be determined whether this activation can arise solely from sterile signals, such as injured tissues or, in many cases, really signifies activation by means of undetected endogenous or exogenous pathogen ligands.\textsuperscript{12}

Evolution did not anticipate the successes of current surgical care or exogenous resuscitation or organ system support and antimicrobial therapies. Many mechanisms of the host response to localized and systemic inflammation have been defined at the molecular level, and recent summaries of these insights relevant to surgical patients have been published.\textsuperscript{13–16} We are also increasingly aware of important endogenous variables unique to the individual host. These include, among others, the problems of confounding conditions or treatments and ageing influences, in addition to less overt influences arising from genetic variation. Each of these components contributes to variability in the expressed phenotype of individual patients. In this review, some insights from molecular investigations of inflammatory processes are discussed in the context of host-specific factors and clinical management practices in surgical patients with an acquired infection. The discussion briefly outlines conserved innate immune and neuroendocrine system responses that may transiently restore destabilizing insults.

Acute stressful conditions often precede the secondary insult of pathogen invasion in surgical patients. As a consequence, the so-called “two-hit” model of inflammatory insult has become the commonly accepted paradigm for stressful injury. We are cognizant that the second hit may be sterile or pathogen induced in nature. Although the secondary insult in the context of SIRS is generally perceived to occur 1 or more days after the initial insult, some have suggested that a demonstrable secondary host response may be elicited within a matter of hours after the initial traumatic event.\textsuperscript{9} Most prevailing models of secondary insult disregard the role of unknown variables in considering how intrinsic regulatory signals, as well as pathogen virulence, interact during ongoing stress. The discussions in this article address the question as to how an existing non–pathogen-induced stress receives signals from endogenous (patient specific) and exogenous (treatment or pathogen) influences that modify the phenotypes and outcomes of an acquired infection.

**LOCAL INFLAMMATORY SIGNALS**

In mounting a defense against invasion by foreign organisms, the innate immune responses may well destroy injured and normal tissues and delay processes of wound repair and resolution of inflammation. To facilitate this immune activation, escalation, and resolution, Nathan\textsuperscript{17,18} has described a “go-no go” binary information flow between immune cells and injured tissues as a necessary command and control system. The reader is referred to his outstanding discussions for greater detail.\textsuperscript{17,18} Tissue molecular signals directing the resolution of localized inflammation are also programmed at an early juncture,\textsuperscript{19} although the regulation of these processes during systemic inflammatory conditions is unclear. Contemporary injury science is seeking to define how host recognition systems distinguish and differentially respond to the states of sterile and nonsterile insult.

The immune response to tissue damage must propagate this information within the injury site against a background of systemic inflammatory responses that have potential to disrupt this controlled information exchange and cellular reprogramming.\textsuperscript{20}
A significant injury focus is not isolated from systemic endogenous signals that modulate tissue blood flow, cellular metabolism, and what are early containment-enforcing anti-inflammatory signals. The host receives input signals regarding the status of the injury site(s) by means of a combination of soluble and “hard-wired” information channels. This bidirectional information exchange is conveyed by several classes of soluble mediators and by direct neural tissue sensing of mediators at local sites.21–24

THE RESPONSE TO THE INITIAL INSULT

Manifestations of the Initial Insult

There may be little evidence of a systemic response in subjects with mild or modest injury.3 An insult of sufficient magnitude to induce several SIRS criteria induces systemic responses that encompass many features of a proinflammatory state, including activation of the coagulation and complement cascades, in addition to leukocyte and endothelial cell activation. Munford and Pughin23 have discussed the temporal dynamics of this initial proinflammatory systemic response that evolves in short order to become anti-inflammatory in nature.

The Neuroendocrine Response

Activation of the hypothalamic-pituitary-adrenal axis (HPA) is the classic neuroendocrine response to stressors, including sterile tissue injury, hypoperfusion, or pathogen invasion.25,26 In a previously healthy host, the initial injury-induced HPA activation elicits a hypermetabolic response and serves to maintain hemodynamic stability acutely, facilitate reprogramming of acute-phase proteins, and exert anti-inflammatory activity. Importantly, HPA activation also promotes an early systemic net anti-inflammatory signal as reflected in reduced levels of several proinflammatory mediators or priming of immune cells for production of anti-inflammatory molecules, such as interleukin (IL)-10.11 The duration of these HPA-induced anti-inflammatory signals seems to be limited, however, and they probably dissipate within a few hours to days after the initial insult.10,11

Neuroendocrine system activation also includes several recently identified peptides that may act in parallel to HPA-derived signals and serve as bridging signals to adaptive immune generation.27 These anti-inflammatory peptides act, in part, by way of the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling pathway and are inducible by infectious ligands. The durability of signaling by means of these neuropeptides in the context of ongoing severe inflammation is largely unknown, but they may serve as an alternative anti-inflammatory mechanism as the influence of other HPA-derived signals wanes.

Signals for Innate Immune System Activation

As noted previously, the innate immune system is initially activated at the local tissue injury site. Resident cells initiate this response and amplify signals for further recruitment of neutrophils and macrophages. These cells express cell surface pattern recognition receptors (PRRs) that detect invariant conserved molecular patterns and foreign nucleic acid structures, allowing the detection of a wide range of microbial pathogens. There are several PRR families that have been identified28 as signal transducers for threatening exogenous (extra- and intracellular pathogen) molecules and endogenous (nonviable or injured tissue) products. The well-described Toll-like receptors serving these functions also interact with more recently defined intracellular signaling molecules, such as nucleotide oligomerization domain (NOD)-like receptors (NLRs) and a multiprotein cellular complex (inflammasome) that activates cellular caspsases.29
These later mechanisms lend potential breadth and intensity to the innate inflammatory repertoire, although, again, the activity of NLRs and the inflammasome pathways have not been well described during conditions of sustained stress.30,31

During conditions of sterile injury, the cognate ligands for PRRs include diverse products of disrupted cells, including, among others, heat shock proteins, mitochondrial peptides bearing the N-formyl group, hyaluronic acid, and the transcription factor HMGB1.17,18,30,31 The Toll-family receptors are increasingly implicated as receptors for these ligands.29,32

In many cases, the early systemic responses to sterile injury are indistinguishable from those arising from infection and many of the same cellular activation events are observed.33 This is not surprising, given that signals derived from tissue injury and infection converge on the same receptors. Hence, a major consideration is how the immune system recognizes such non–pathogen-induced signals29 and provides informational cues that constrain the more damaging inflammatory responses invoked by microbial invasion.17

Rhythms After the First Hit

Homeostasis exhibits rhythmic physiologic and biochemical activities. The temporal predictability of this endogenous control is presumed to confer acute adaptive advantages34 that likely extend to modulating systemic illnesses and solid organ function35 over extended periods.

Circadian entrainment

The molecular regulatory components of the circadian clock36 generate synchronization that coordinates phase relations among numerous internal rhythms.37 Indeed, many gene products of the core circadian clock are embedded in regulatory networks necessary for normal cell function.38 During health, circadian rhythms entrained by light and dark and food intake cycles are readily detectable as neuroendocrine secretory and autonomic activities, including heart rate and blood pressure.

As discussed elsewhere in this article, these entrainment cues are frequently altered in stressed hospitalized patients, and the consequences of this loss of environmental cues have yet to be fully defined in the context of stress.39 Recent data document that inflammation-inducing ligands, including endotoxin40 and tumor necrosis factor-α (TNFα),41 suppress the expression of clock regulatory genes in the suprachiasmatic nucleus and in peripheral tissues. This linkage of innate immune system activation to circadian rhythm control has yet to be explored in the setting of persistent systemic inflammation.

Autonomic rhythms

Autonomic function also exhibits circadian rhythmicity as assessed by measures of heart rate variability (HRV).42 This daily fluctuation in frequency and power spectra has implications for sympathetic and parasympathetic balance and the acute regulation of systemic inflammatory activity. Autonomic imbalance, reflected by sympathetic activity excess (or parasympathetic attenuation), is associated with increased morbidity in patients who have severe sepsis.43 A reduction in parasympathetic activity may be associated with diminished capacity to exert vagal cholinergic control over proinflammatory mediator activity.44 Reductions in implied vagal nerve activity have now been noted during inflammatory conditions associated with endotoxinemic conditions in humans45 and in experimental conditions of sterile systemic inflammation.46 Hence, continued attenuation of vagal activity during SIRS may impede this alternative mechanism for controlling inflammatory balance.
**Endocrine rhythms**
The secretion of endocrine hormones is also subject to circadian rhythms and to intermittent stimuli, such as feeding and emotion. As detailed elsewhere, a characteristically enhanced endocrine hormone profile is elicited during the early-phase response to injury or infection. These hormone signals promote acute-phase metabolic and immunologic programming of target tissues.

**Pathogens of the Initial Insult**
Comprehensive discussions of the spectrum of initial pathogens complicating surgical illnesses are provided elsewhere in this issue. The reader is also referred to recent overviews of pathogen recognition mechanisms and discussion of virulence acquisition and to discussions of plausible genetic determinants of pathogen recognition and immune responsiveness. Most such reports do not, however, discuss these factors in the context of an existing non–pathogen-induced host response.

**Modifiers of the Initial Injury Response**
A healthy person subjected to an acute insult relies on stereotypic responses to recognize, contain, and resolve local sites of injury or pathogen invasion. The concept of a prototypical “healthy” host response must, however, be modified by patient-specific (endogenous) factors, some of which are discussed elsewhere in this article (Fig. 1). It can be conjectured that initial host responses are more influenced by these

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**Fig. 1.** The host response to an initial sterile “hit” (stress), such as trauma or surgery, includes activation of inflammation-responsive systems (eg, innate immune system) modified primarily by the magnitude of insult and patient-specific (endogenous) factors. As the systemic inflammatory response arising from an initial stress continues, patient management and pathogen virulence (exogenous factors) assume a more prominent influence on the balance of systems activity. Responses lower than the basal level generally reflect reduced end-organ responsiveness (tolerance) and reduced signal input variance (adaptability). The interactions between endogenous and exogenous factors lead to uncertainty (gray area) over time about systems activity and overall responsiveness to secondary insults, such as infection.
endogenous host-specific factors than during later phases of SIRS, when therapies or interventions, iatrogenic misadventure, and diminished host adaptability become more consequential.

**Age**

More than 50% of patients receiving intensive care are older than 65 years of age.\(^1\) Advancing age is clearly associated with increased morbidity and mortality. The relation between age-related immune competence and confounding illness is, however, more complex than commonly appreciated.\(^54,55\) Epidemiologic data attest to the concept of “immuno-ageing,” wherein proinflammatory innate immune responsiveness is reasonably well preserved among many older subjects.\(^56\) The ageing population exhibits increased cytokine markers of low-grade inflammation (eg, IL-6), and this is associated with increased risk for development of infection\(^57\) and other stressful events.\(^58\) Elderly subjects challenged with lipopolysaccharide (LPS) also exhibit a more prolonged febrile response and hypotension,\(^56,59,60\) in addition to prolonged and enhanced cytokine responses during pneumococcal pneumonia.\(^61\)

Although some theories of ageing suggest that innate immune response capacity is sustained, at least in part, by the accumulated influences of noxious challenges, such as oxidative stress,\(^62\) there may be other interacting factors that promote proinflammatory competence during ageing. For instance, the diminution of autonomic variability, particularly of vagal activity, that accompanies advancing age\(^42\) may promote enhanced TNF\(_\alpha\) activity during initial stress. By contrast, physical conditioning enhances parasympathetic system signaling and provides a survival advantage to physically fit elderly patients during acute inflammatory stress by attenuating cytokine excesses.

The process of immunosenescence, or age-related defects in the human immune system, affects principally the adaptive immune response.\(^55,56\) There is a gradual loss of T-cell repertoire from naive CD8 T cells and reduced response to neoantigens in elderly subjects. Concomitantly, there is a gradual shift from a type 1 cytokine response (eg, IL-2, interferon-\(\gamma\) [IFN\(_\gamma\)], TNF\(_\alpha\)) toward a type 2 response (eg, IL-4, IL-6, IL-10, IL-15) that further impairs cell-mediated immunity.

**Gender**

It is widely assumed that gender influences the initial inflammatory response and risk profile resulting from injury. A discussion of the possible mechanisms underlying this canon is extensively presented elsewhere.\(^63,64\) Nevertheless, recent single-institution reports,\(^65\) multi-institutional prospective studies,\(^66,67\) and report compilations\(^68\) question the validity of the assumed female gender benefit among trauma patients. There are also conflicting reports regarding gender-based responses to lesser inflammatory challenges, such as to endotoxin.\(^69,70\) Suffice it to say that, at present, there are no consistent gender-specific differences in systemic inflammatory responses reported among humans subjected to an initial sterile or pathogen-induced stress.

**Confounding Illness and Treatment**

There has been surprisingly little prospective correlation of acute inflammatory responses among noncardiac surgical patients that has carefully assessed the influence of confounding illnesses. Indeed, the precise classification of relevant confounding illness remains in flux.\(^54\) Pittet and colleagues\(^71\) noted several preexisting conditions that influenced the outcome of bacteremia in surgical patients, including, among others, recent surgery, antibiotic therapy, and previous cardiogenic shock or resuscitation. However dated this observation may be, the importance of such
conditions suggests that a recent systemic inflammatory condition may predispose to infection and adversely influence outcome.

**Genetic Factors**

Inheritance contributes to the risk for premature life-threatening infection. Although the mechanisms for this increased risk are not defined, there are identifiable low- and high-inflammatory cytokine response patterns among random subjects and a strong genetic linkage for stimulated cytokine production among monozygotic twins. Genome manipulations in animals clearly suggest that genetic variation within key cell signaling or response pathways may alter local and systemic innate and adaptive immune responses. Genetic variation within homologous loci among humans is also likely to influence the host capacity to recognize and resolve tissue inflammation or respond to pathogen invasion. Genetic variation may also contribute to the expressed magnitude and duration of the SIRS phenotype, as suggested, for example, by variable cholinesterase activities and the resultant response to endotoxin.

**Initial Interventions**

**Resuscitation**

It is recognized that fluid resuscitation modifies host inflammatory responses to infectious or noninfectious insults. Variations in fluid resuscitation regimens also result in varying inflammatory responses among older patients. It is presently unknown if these initial resuscitation-modified inflammatory changes influence later immune, endocrine, and autonomic capacities during later phases of the SIRS condition. Substantial information regarding some of these issues may be forthcoming when detailed analyses of large multi-institutional studies are reported.

**Antimicrobial therapy**

As discussed elsewhere in this issue, there is little doubt that inappropriate use of antimicrobial therapies increases the risk for overall infection and the emergence of resistant organisms. The use of prophylactic agents in patients with initial sterile stress has received limited study as to systemic inflammatory responses. It is clear, however, that inadequate antimicrobial therapy independently increases outcome risk among patients who have SIRS and develop nosocomial infection. This adverse effect is likely enhanced among surgical patients who have complex illness.

**RESPONSES TO SUBSEQUENT INSULTS**

The components of host response from an initial insult are more clearly defined than are those resulting from secondary events (see Fig. 1). The various clinical phenotypes and outcome trajectories resulting from prolonged stress in conjunction with infection have been debated for years. Several prominent overviews of this complex topic have been published. Although a de novo infectious challenge, in and of itself, yields variation in early host responses, the later phases of SIRS promote an even broader palate of functional system(s) phenotypes as intervention-related influences interact with endogenous determinants. There may be conflicting signals being transmitted in parallel and, in some cases, isolation of tissues from the normal feedback controls of the uncomplicated state. Persistent proinflammatory activity is manifest, for example, by continued coagulation system activation, even as other markers of proinflammatory activity may be waning. Simultaneously, variations in the competence of innate and adaptive immune defenses become evident within some tissue sites.
and diminished capacity for neoantigen responses are more thoroughly discussed elsewhere.\textsuperscript{21,96} An important feature of SIRS is a persistent acute-phase response that experimental studies suggest may modify immune competence and solid organ function.\textsuperscript{97–99} In the context of ongoing inflammation, altered innate immune competence may occur by means of gene-silencing programs or other mechanisms.\textsuperscript{20,29,100}

**Altered Rhythms During the Secondary Insult**

Not infrequently, a prolonged stress state manifests diminishing amplitude, frequency, and efficiency of autonomic and neuroendocrine signaling.\textsuperscript{91,101} For example, there have been several reports documenting diminished time domain measures of HRV among critically ill infected and injured patients\textsuperscript{43,102–105} that correlate to increased solid organ dysfunction and mortality risk. Reduced host adaptability, as reflected in such measures of total power, may serve as a surrogate marker of organ systems’ “connectedness” and of overall host capacity to respond effectively to inflammatory stressors.\textsuperscript{101,106}

Disturbances in short-term variability and longer term circadian rhythmicity of neuroendocrine hormone secretion are also observed during prolonged inflammatory illness.\textsuperscript{48,49} Attenuated hormone rhythmicity and signal amplitude are known to associate with ischemic events\textsuperscript{47} and may likewise contribute to disordered metabolic and immune functions.\textsuperscript{39,48,49} An intriguing association of reduced cardiac rate variability to adrenal cortical tolerance (or relative insufficiency) has been noted in some injured patients.\textsuperscript{107}

**Pathogens of the Second Hit**

The SIRS state promotes loss of adaptive immune surveillance that likely enhances virulence factor acquisition in some bacterial species.\textsuperscript{21,50,108} Although de novo infection may elicit distinctive gene expression patterns within immune cells,\textsuperscript{109,110} immune cell expression signatures during acquired infections seem to converge during ongoing inflammation.\textsuperscript{111–113} These observations suggest that a diminished immune system repertoire (variability) reflects another aspect of altered host adaptability.

**MODIFIERS OF THE SECONDARY INSULT**

**Age**

Age-related diminutions of immune and endocrine functions\textsuperscript{114} and autonomic signal attenuation may all contribute to adverse outcomes among elderly patients. There is currently limited insight across the age spectrum as to how prominently these endogenous factors contribute to loss of adaptability during prolonged stress.

**Genetic Factors**

Most genetic association studies within seriously ill patients have been reported from mixed populations of community-acquired and nosocomial infections. The caveats for deriving definitive conclusions from existing clinical gene association studies have been discussed.\textsuperscript{51,53} Nevertheless, there have been some single-institution prospective studies of highly stressed at-risk surgical populations, such as those with trauma and burns, that are highly suggestive of genetic contribution to nosocomial infectious risk. For example, functional single-nucleotide polymorphisms of proinflammatory cytokines\textsuperscript{51,115–117} and pathogen recognition receptors\textsuperscript{116,118} repeatedly associate with enhanced infection risk in stressed patients. Interestingly, these polymorphisms do not overtly modulate human responses\textsuperscript{119} during health but only seem to enhance risk and alter responses in the context of ongoing stress.
THE INFLUENCES OF CURRENT TREATMENT PRACTICES

Little is known about how currently “acceptable” treatment practices (exogenous factors) might alter host adaptability. Several such strategies have been adopted after prospective demonstrations of improved outcomes that also exhibited some diminution of inflammatory markers. Interestingly, most of these adopted support modalities are designed to reduce signal input variance to the stressed host. Several current management practices are briefly discussed to speculate as to how invariant clinical management practices might alter the phenotypes and systemic responses of stressed patients.

Mechanical Ventilation

Current management of respiratory failure generally conforms to protective strategies that impose constraints to variations in volume, pressure, or oxygenation parameters. These approaches seem to promote the resolution of initial pulmonary inflammation and related organ system dysfunction. How these management practices influence inflammatory responses to a later tissue injury or infection challenge remains a matter of some conjecture.

Glucose Control

The clinical management concept of rigid glucose level control (reduced variability) has been rapidly adopted by the intensivist community. There is now some reconsideration of this rigorous protocol, and the issue of how varying ranges of glucose and insulin control may modulate inflammatory responses remains open to question.

Route and Composition of Feeding

The use of parenteral nutrition has greatly diminished as a management practice among stressed patients. Several inflammatory mediator responses may be potentiated during continuous parenteral feeding. Some data suggest that these enhanced responses may be related to the composition of parenteral feeding regimens. Importantly, continuous enteral or parenteral feeding may dampen cellular and systemic regulatory signals exerted by autonomic and circadian rhythms. Hence, alternative management strategies designed to enhance variability of nutrient provision might further leverage any benefits of nutritional support.

REFERENCES


