Posttraumatic Inflammation Is a Complex Response Based on the Pathological Expression of the Nervous, Immune, and Endocrine Functional Systems

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The successive phases that make up both the local and systemic posttraumatic acute inflammatory response could represent the expression of three concatenated pathological or "primitive" functional systems with trophic properties: the nervous, immune, and endocrine ones. The nervous functional system would play an important role in the phenomenon of ischemia-reperfusion, which would be represented by nutrition by diffusion that is either anaerobic (ischemia) or with defective use of oxygen (reperfusion) and, thus, with a limited energy requirement. The immune functional system would be represented by the infiltration of the tissues by inflammatory cells and bacteria, which would become mediators in providing nutrition to the injured tissues. Although the use of oxygen would still be defective, hypermetabolism and fever would occur. In these inflammatory response phases, the lymphatic is the most important circulation. The endocrine functional system would be the most specialized and would have high energy requirements because it would be represented by the blood capillary-mediated nutrition. Highly specialized epithelial cells would already possess a perfected oxidative metabolism. The successive expression of these three functional systems during embryonic development and also during the evolutionary development of our species could explain why the inflammatory response is a ubiquitous mechanism that is common to multiple diseases, because it is an integrator of the ontogeny and phylogeny. Exp Biol Med 229:170–181, 2004

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In the days of John Hunter (1728–1793), research was mainly descriptive, or it was aimed at interpreting the meaning of inflammation in terms of the whole body (1). Nowadays this objective is still valid, despite continuous research being performed on the inflammatory response. Thus, Böttiger explains, "we need integrative biology and integrative physiology to integrate all new knowledge into an understanding of whole tissues, organs and individuals" (2) because an "increasing distance between new molecular knowledge and everyday patient care" is being produced (2).

A new interpretation of the response to injury by the nervous, immune, and endocrine systems could represent a way to integrate biochemical knowledge into clinical practice. The discovery that the signal molecules of the nervous, immune, and endocrine systems (i.e., neurotransmitters, cytokines, and hormones, respectively) are expressed and perceived by the three systems (3–5) has already led to a different concept of these systems.

At present, it is clear that nervous, immune and endocrine mechanisms can affect each other. Thus, immune, endocrine, or neural cells can express receptors for cytokines, hormones, neurotransmitters, and neuropeptides; immune and neuroendocrine products coexist in lymphoid, endocrine, and neural tissue; endocrine and neural mediators can affect the immune system; and immune mediators can affect endocrine and neural structures (6).

At present, the nervous, immune, and endocrine systems, which have been considered as separate "systems," can be considered components of a single, integrated defense mechanism in which the interactions between systems are as important to understanding adaptation as the interactions within a system (4). If so, studying the

response of this single, integrated defense mechanism of the body when exposed to an old stimulus, such as mechanical energy, could be a method for learning about the interactions that exist between these three systems (7).

Different types of vascular pathology are the results of the actions of both acute and chronic mechanical energy in the body. Specifically, these types of energy can stimulate the endothelium, which owing to its strategic position, plays an exceedingly important role in regulating the vascular system by integrating diverse mechanical and biochemical signals (8–11) and responding to them through the release of vasoactive substances such as cytokines and growth factors (8–10).

Mechanical energy is obviously involved in the etiopathogeny of mechanical traumatisms and can produce a local response, such as acute inflammation (12), or a generalized one, as occurs in a patient with polytrauma (13). We have proposed that both the local and systemic responses are based on the successive functional predominance of the nervous, immune, and endocrine systems. This hypothesis implies that the final and prevalent functions of these systems may represent the consecutive phases of the response to stress developed by a single system: the psycho-neuro-immune-endocrine one (7, 14–16).

Nervous, immune, and endocrine functions seem to be balanced in physiological situations. However, when a traumatic injury occurs, one of these functions predominates in time in relationship to the remaining two, and their expression is not normal or physiological, but rather, they acquire a clearly pathological character. Thus, traumatic injury seems to cause a response that is predominantly nervous at first, then immune, and finally, endocrine (15, 16).

If we consider that these functions are expressed by the endothelium and, by extension, by the vascular wall, the posttraumatic local inflammatory response would have three phases. The first phase would be a nervous, or immediate phase, with vasoconstriction and vasodilation (12, 17), which includes reperfusion injury and exudation secondary to an increase of endothelial permeability that is the cause of swelling (18). The second phase is an immune, or intermediate phase, with diapedesis or cell migration of leukocytes (12, 19–21), which is associated with coagulation (22) and phagocytosis. Finally, there is an endocrine or late phase, which is characterized by angiogenesis with endothelium and vascular wall modeling (22–25), which in healing, involves tissue regeneration or wound repair (Fig. 1; Refs. 12, 16).

This extensive concept of the inflammatory response shows significant differences with its limited initial description. Local acute inflammation has been studied since ancient times. Aulis Cornelius Celsus (25 B.C.–50 A.D.) described the four cardinal signs of acute inflammations as *rubor et tumor cum calore et dolore* (7, 26), and John Hunter (1728–1793), who was one of the first investigators to perform a scientific study of inflammation, describes them as erythema, edema, heat, and pain (7, 12, 26). However, these signs principally correspond to the hypothetical nervous or immediate phase of the inflammatory response, which is followed by the immune or intermediate phase with leukocyte recruitment.

Elie Metchnikoff (1845–1916) first described cellular immunity with phagocytosis and the destruction of microbes (26), but the inflammatory response seems to include more than an effective host defense mechanism with the elimination of necrotic tissue, foreign material, and bacteria (21). Growing evidence suggests that these processes, which make up the immune or intermediate hypothetical phase of the inflammatory response, seem to give rise to *restitutio ad integrum*, and, in its defect, collagenous scar formation (12, 21, 25, 27), both processes forming the endocrine or late phase of inflammation (15, 16).

Lawrence (12) considers that various processes involved in wound healing occur at predictable time points after injury and, thus, that the healing process can be divided into early, intermediate, late, and final phases. Each phase is characterized by specific biological processes: the early phase involves inflammation and creation of hemostasis by blood coagulation and platelet aggregation; the intermediate phase consists of mesenchymal cell proliferation and migration, epithelialization, and angiogenesis; the late phase includes synthesis of collagen and other matrix proteins and wound contraction; and remodeling predominates in the final phase of wound healing (12).

However, other authors (28) consider that a highly regulated cascade of events is involved in the complex process of wound repair. These events can be divided into three stages: a hemostatic phase with formation of a hemostatic plug; an inflammatory phase that can begin as early as 6 hours after injury with neutrophils and monocytes, which leave the circulation to debride devitalized tissue and phagocytose infectious agents and other foreign bodies; and, finally, the proliferative phase with keratinocytes restoring surface integrity, mesenchymal cell migration and the deposit of an extracellular matrix, angiogenesis, and tissue remodeling. This last phase, or proliferative phase, is long because tissue remodeling that begins from the moment of injury continues for several months or even years after the wound has apparently healed (28).

Therefore, with progressive knowledge of the inflammatory response, its concept and complexity have been successively increasing, which in turn, may imply the requirement of a novel definition (21). This is the objective of this new interpretation of inflammation, which is based on the successive pathological expression of the nervous, immune, and endocrine functional systems (15, 16).

These systems would be fundamental in wound healing in three interrelated functional phases (Fig. 1). The first is a nervous phase with vasoconstriction and vasodilation that causes early ischemia-reperfusion, although its persistent vasodilator effect progressively decreases during the inflammatory response. One consequence of the ischemia is production of cellular edema due to loss of cellular ionic

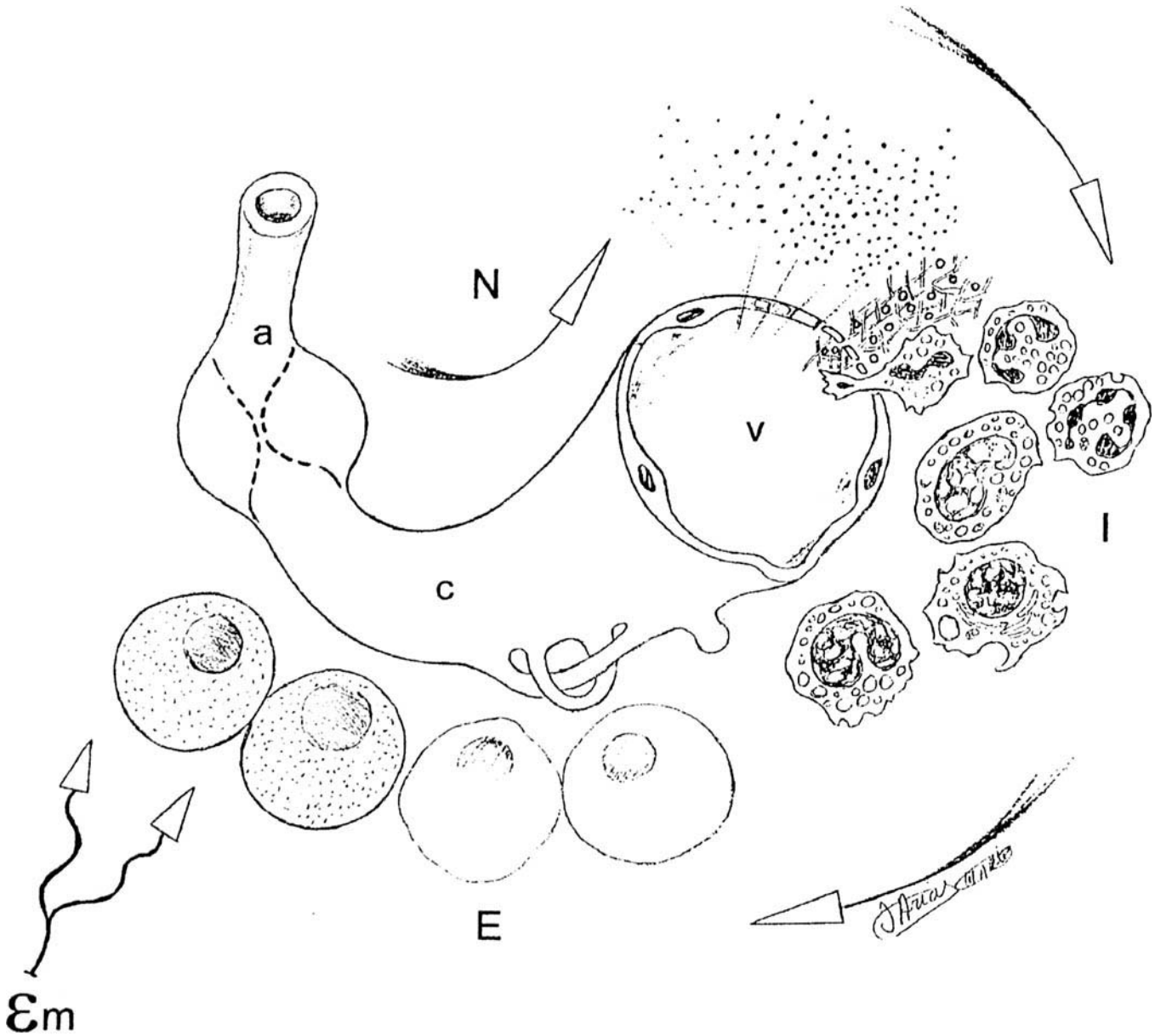

Figure 1. Posttraumatic inflammatory response. The succession of three functional systems that have the common feature of possessing a nutritional purpose would characterize this response to aggression by mechanical energy (εm). In the nervous functional system (N), the phenomenon of ischemia-revascularization secondary to arteriolar vasomotor activity (a) (vasoconstriction-vasodilatation) would produce interstitial edema and thus permit selective cellular nutrition by diffusion. In the immune functional system (I), the blood loses its characteristic of liquid tissue due to coagulation and digestion, both extracellular (enzymes) and intracellular (phagocytosis) debris and bacteria are produced by venular diapedesis (v) of the inflammatory cells, which may become intermediary cells of the nutrition of the injured tissue. In the endocrine functional system (E), finally, vessel-mediated nutrition develops, and angiogenesis originates the new capillary network (c), which permits both regeneration as well as healing.

homeostasis. This is associated with oxidative stress, hydrolase activation, mitochondrial dysfunction, ATP depletion, and acidosis. These abnormalities may progress, causing cellular necrosis or, to the contrary, the process may revert after reoxygenation (29).

There is evidence that reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and hydrogen peroxide, contribute to reperfusion injury of the previously ischemic tissue (30, 31). It has been proposed that transmembrane ion gradients are dissipated in the course of ischemia, allowing elevated cytosolic concentrations of calcium. This in turn activates a protease that irreversibly converts xanthine dehydrogenase, which predominates *in vivo*, into xanthine oxidase. Concurrently, cellular ATP is catabolized to hypoxanthine, which accumulates. On reperfusion, readmitted oxygen, hypoxanthine, and xanthine oxidase combine to generate superoxide and hydrogen peroxide. This ROS can interact to yield a range of cytotoxic agents, including hydroxyl radicals (30, 31).

Generation of ROS during either ischemia or reperfusion has been directly demonstrated using electron paramagnetic resonance spectroscopy and chemiluminescence.

Table 1. Posttraumatic Local Acute Inflammatory Response

Nervous phase	Sensitive:	
	–Pain	Inflammatory pain
	–Analgesia	Posttraumatic analgesia
	Motor:	
	–Contraction	Ischemia → Cellular edema
	–Relaxation	Reperfusion → Interstitial edema
Immune phase	Tissue infiltration:	
	–Molecular	
	• Proteins	
	–Fibrinogen	Fibrin matrix
	–Cellular	
	• Platelets	Clot
	• Neutrophils	Intra- and extracellular digestion:
	• Macrophages	• Necrotic tissue
	• Lymphocytes	• Foreign material
	–Bacterial	• Contamination
		• Infection
Endocrine phase	–Epithelial cells	–Epithelial cell regeneration
	• Angiogenesis	
		–Fibroblast scar formation
	Maturation	Tissue remodeling

In principle, ROS may injure cells by causing peroxidation of membrane lipids, denaturation of proteins including enzymes and ion channels, and by causing strand breaks in DNA (32).

There is an increase of endothelial permeability in most forms of ischemia-reperfusion injury. Capillary leak is mediated by ROS and also by the release of histamine, eicosanoids, and tryptases by perivascular mast cells (33). There is an additional influence of kinins, thrombin, and the complement system (C_{3a} and C_{5a}; Ref. 34). Fluid extravasation is the cause of interstitial edema (Table 1).

The second phase of the inflammatory response is considered an immune phase. In this evolutionary state of inflammation, cellular infiltration (platelets and leukocytes), and, in most of the cases, bacterial contamination are added to the molecular (water, proteins) infiltration of the injured tissue. In addition, a liquid tissue, blood, loses this quality in its new invasive activity because of the coagulation process (Table 1).

Recent research into ischemia-reperfusion injury has focused on the vasculature, especially on leukocyte-endothelial cell interactions, which are relevant to many vascular diseases (31, 35). Leukocyte migration is stimulated by collagen; elastin breakdown products; complement factors; and immunomodulatory factors including transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, interleukin (IL)-1, platelet-derived growth factor (PDGF), leukotriene B_4, and platelet factor IV (12, 34). The sequence of events that allows leukocytes to travel to the sites of host defense is designed as the multistep paradigm of leukocyte recruitment (36). It involves three major steps: rolling, firm adhesion, and transendothelial migration (37).

Rolling is mediated by the interactions of E and P selectins on activated endothelial cells and leukocyte L selectin. Firm adhesion is mediated by interaction of leukocyte surface integrins with molecules of the immunoglobulin gene superfamily expressed on the endothelium. The immunoglobulin gene superfamily ligands are intercellular adhesion molecule-1 (ICAM-1) and ICAM-2 for the β_2-integrins, vascular cell adhesion molecule (VCAM)-1 for very late antigen-4 and $\alpha_9\beta_1$, and the mucosal addressin cell adhesion molecule-1 for $\alpha_4\beta_7$. Transendothelial migration involves diapedesis by leukocyte integrin receptor interaction with endothelial ligands of the immunoglobulin gene superfamily and migration through the subendothelial matrix by platelet-endothelial cell adhesion molecule (PECAM)-1 expression (37).

The accumulated leukocytes bound to the adherent platelets may promote fibrin deposition, thereby contributing to thrombus formation. Adhesion of activated platelets to endothelium is also capable of both initiating and amplifying leukocyte recruitment, providing a link between thrombosis and inflammation (Table 1; Ref. 37).

Activated neutrophils and macrophages initiate cellular wound debridement by phagocytosing bacteria and foreign material. After binding, bacteria and debris are engulfed and digested by oxygen radicals and hydrolytic enzymes within the inflammatory cells (12, 34). Furthermore, neutrophils and macrophages contribute to the extracellular breakdown by releasing matrix metalloproteinases such as collagenase and elastase in response to chemoattractant stimulation, and these enzymes are involved in this migration as well (12, 34).

Most of the vascular inflammatory responses are mediated through the IκB/nuclear factor (NF)-κB system.

The expression of inducible genes leading to the synthesis of cytokines—the chemokines, adhesion molecules, and autacoids—relies on transcription factors. Among the primary transcription factors, NF-κB plays a central role in the regulation of inflammatory mediators (38, 39).

NF-κB activation in leukocytes recruited during the onset of inflammation is associated with proinflammatory gene expression, whereas such activation during the resolution of inflammation is associated with expression of anti-inflammatory genes and induction of apoptosis (39, 40).

During this immune phase, inflammation progresses through the action of proinflammatory cytokines, including IL-1, TNF-α, gamma-interferon, IL-12, IL-18, and granulocyte-macrophage colony-stimulating factor, and is resolved by anti-inflammatory cytokines such as IL-4, IL-10, IL-13, alpha-interferon and TGF-β (33, 34, 40, 41), and by antimicrobial peptides such as defensins and cathelicidins (33, 42).

Fresh neutrophils no longer enter the site, and those present undergo apoptosis. In addition, macrophages ingest apoptotic neutrophils and degrade their residual stores of elastase (12, 34). Phagocytosis of apoptotic cells decreases macrophage activation and cytokine production through secretion of TGF-β. Monocyte and macrophages emigrate in the local lymph nodes. During this migratory process, monocytes differentiate into dendritic cells, up-regulating HLA class II antigen membrane expression and acquiring costimulatory molecules such as CD80 and CD86. These cells might then present antigenic peptides to lymphocytes, contributing to the generation of a greater immune response (43). T lymphocytes play a crucial role in normal healing and are present in maximum concentrations 5 to 7 days after injury (Table 1; Refs. 34, 44, 45).

Finally, there is an endocrine phase. Its expression predominates for a long time in order to achieve repair and remodeling of the newly developed tissue. Angiogenesis is the process common to scarring and regeneration. The expression of the angiogenic phenotype is a complex process that requires a number of cellular and molecular events to occur in both a spatial and temporal pattern (45).

In this evolutionary state, the coordination of angiogenesis and inflammation is achieved by the ability of both endothelial cells and leukocytes to respond to common stimuli such as chemokines (46). During wound healing, angiogenic chemokines exert both a direct role on endothelium and an indirect role on angiogenic factor-expressing leukocytes to induce neovascularization of the granulation tissue. Conversely, expression and distribution of angiostatic chemokines strongly correlate with the onset of angiostasis and the attenuation of the angiogenic phase (46).

The initial vasodilatation of existing vessels is accompanied by increases in permeability and degradation of the surrounding matrix, which allows activated and proliferating endothelial cells to migrate and form lumen (45, 47). Degradation of the extracellular matrix involves an array of proteinases that not only provide "room" for the migrating cells but also results in the release of growth factors, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF)-1 (47).

Largely in response to nitric oxide (NO), vasodilation is one of the earliest steps in angiogenesis. VEGF, which is transcriptionally upregulated in part by NO, mediates an increase in vascular permeability, and which is accomplished through redistribution of intercellular adhesion molecules, including PECAM-1 and vascular endothelial (VE)-cadherin, and alterations in cell membrane structure via induction of a series of kinases (47, 48).

Macrophages have long been known to participate in the induction of new blood vessel growth in a number of different settings, including wound healing (45). Macrophage-produced cytokines are involved in angiogenesis, fibroblast migration and proliferation, collagen production, and possibly, wound contraction. TGF-β, IL-1, bFGF, IGF-1, and PDGF are several of the most critical macrophage-derived cytokines (34). Angiopoietins are also important vascular regulatory molecules involved in vessel formation that act in synergy with other angiogenic molecules such as bFGF, IGF-1, and matrix metalloproteinases (46, 47, 49). With maturation of the vascular network, local physiological requirements must be met (Table 1; Refs. 47, 49).

It could be proposed that the principal meaning of these three consecutive phases of the inflammatory response is nutritional in nature. Thus, in the immediate or nervous phase, the ischemia-revascularization phenomenon, on causing edema that is both cellular during ischemia, as well as interstitial during reperfusion, could be interpreted as the expression of a nutritional mechanism by diffusion. Although this cellular nutrition mechanism of the injured tissue is simple, it can be temporally effective (Fig. 1).

The cellular hydration state is an important determinant of cell function and oxidative stress; nutrients and hormones exert their effects on metabolism and gene expression partially via a modification of cell volume. Most importantly, intracellular signal transduction pathways are activated in response to small fluctuations or changes in cell hydration. Thus, cell swelling triggers an anabolic pattern, and cell shrinkage triggers a catabolic pattern of cellular function (50).

During the intermediate or immune phase, the activated inflammatory cells infiltrate the injured tissue by diapedesis to perform digestion functions. These functions are both intracellular in nature, by phagocytosing debris and bacteria, as well as extracellular, in the release of metalloproteinases into the wounded area (Fig. 1; Refs. 12, 34). In a phase in which the blood loses its normal characteristic of liquid tissue due to coagulation, the injured tissue may benefit nutritionally from the digestive functions of the inflammatory cells that infiltrate it.

In the late or endrocrine phase, healing and nutrition are dependent on a functional network of capillary plexus formed by the process called angiogenesis (Fig. 1; Refs. 45–47).

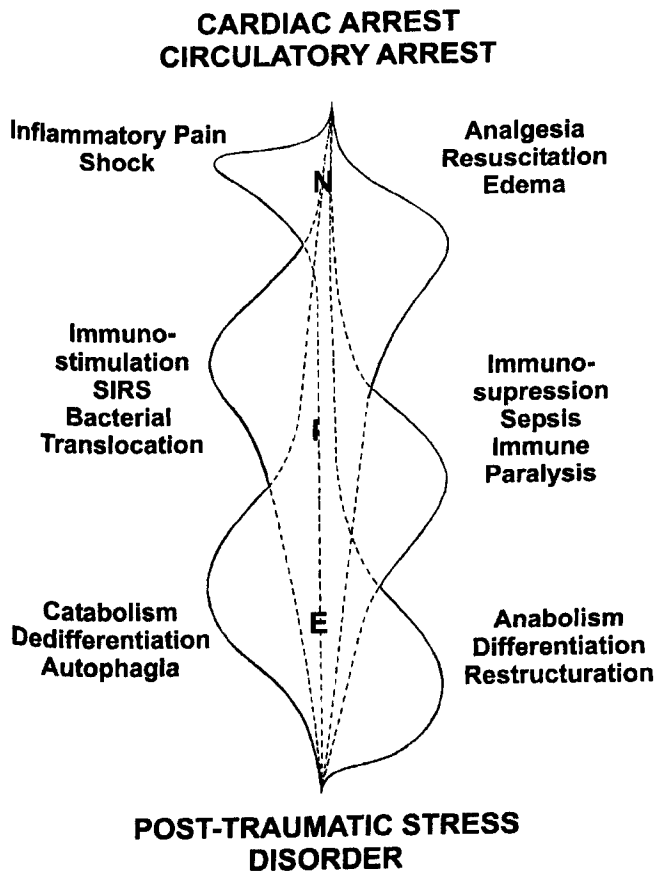

Figure 2. Schematic representation of the systemic response to injury produced by mechanical energy. This response is successively performed by the nervous (N), immune (I), and endocrine (E) functional systems, in a nutritional sense. Normally, the N phase, with cardiovascular instability, lasts for days. Phase I generally occurs with infection or sepsis and generally lasts weeks, and phase E, which includes the convalescence period, lasts months, and post-traumatic stress disorder may be a complication. The incidence of factors that affect the evolution takes the response back to the initial phase (N) and would cause vasodilatory shock and circulatory arrest. SIRS; Systemic Inflammatory Response Syndrome.

These different nutrition mechanisms expressed during the posttraumatic inflammatory response have also been described during embryonic development. From the earliest stages, the embryo develops in the absence of vascularization, receiving its nutrition by diffusion (51). In an orderly and sequential manner, however, the embryo rapidly transforms into a highly vascular organism, survival being dependent on a functional, complex network of capillary plexuses and blood vessels (47).

Furthermore, the posterior incorporation of fibroblasts in an interstitial space also makes it possible to suspect their trophic intermediary capacity between the blood vessels and epithelial cells, elaborating a tissue with specific resistance to oxidative metabolism (45, 46).

In addition, in the systemic response to injury by mechanical energy, as occurs in a patient with polytrauma, the nervous or immediate phase would be represented by shock and generalized ischemia-reperfusion with blood flow redistribution among the body organ systems (52, 53). The immune or intermediate phase would be characterized by the systemic inflammatory response syndrome (SIRS; Ref. 54), and the endocrine or late phase would be represented by catabolism with cachexia or anabolism in the convalescence period (55–58).

Although the duration would be apparently different, the hypothetical similarity of the local and systemic responses to mechanical injury could be attributed to the existence of a general response mechanism to the injury in the body that is based on the successive and predominant expression of the nervous, immune, and endocrine pathological functions (Fig. 2; Refs. 14–16).

Extravascular extension of the inflammatory response increases the type and number of both cells and mediators that are activated. Thus, a more extensive expression of these pathological functional systems is produced after traumatic injury. The functional alterations corresponding to the sensitive, and the motor nervous system as a whole, represent a complex reflex with afferent and efferent pathways (59).

Multiple trauma can be both physical and emotional stressors that exceed a critical threshold and that cause a pathological increase of the stress system (60, 61) with a reflex response in which cortical and subcortical circuits of the central nervous system (CNS) are involved (61, 62). In these patients, the severity of the stressor and the ensuing neural response systems can cause damage or exacerbate preexisting disease processes; that is, the responses can become maladaptive (63).

The afferent system is composed of neural input from multiple receptors, particularly of nociceptors (59, 62). Thus, biphasic pain response is produced after traumatic injury. The first phase of the pain response is brief and correlates with the well-localized initial pain, but it can be further enhanced in a second phase by many tissue-related factors and the inflammatory mediators released. Sensitization of the CNS developed from a cascade of neuroimmune activation events in tissues and in the peripheral and central nervous systems. Among the excitatory mediators that have been described that stand out are glutamate, bradykinin, and products derived from the activation of cyclo-oxygenase 2 and induced nitric oxide synthase (64).

Central sensitization, with hyperalgesia and allodinia, characterizes pathological or inflammatory pain (65–67), one of the four cardinal signs of the inflammation described by Aulis Cornelius Celsus. However, a new response that modulates the pain is also produced through a descending inhibitory pathway that induces analgesia (59). If analgesic treatment is initiated before the noxious stimulus, or preemptive analgesia, the central sensitization could be avoided, and the subsequent pain perception and other untoward effects that can persist beyond the recovery period would be reduced (67, 68).

In traumatic injury, the motor nervous response is associated with the sensitive nervous response and is

characterized by pain and analgesia (Fig. 2). This post-traumatic motor response consists in striated and smooth muscular contraction and relaxation. The skeletal muscle reflexes that are under motor neuron control generally have a defensive character, that is, escape and avoidance of further injury (59).

However, the pathological motor response in which the smooth muscular fiber is prominent, particularly in the vascular system, may be more important (69). Severe vasoconstriction in the peripheral circulation is the normal response to conditions in which arterial pressure is too low for adequate tissue perfusion, such as acute hemorrhagic shock (53, 69, 70). The sympathetic and adrenomedullary (sympathetic) systems, whose increased activation facilitate adaptation and tend to promote homeostasis, are involved in the production of this generalized vascular response (60).

In patients with shock, blood flow is redistributed throughout the organ systems of the body, and perfusion to the heart, brain, and adrenal glands is maintained at the expense of cutaneous, splanchnic, and renal vascular beds (53). A serious complication in marked hypovolemia is circulatory arrest. In this case, although the patient may be pulseless and apneic, the heart may still be beating or attempting to beat. However, cardiac arrest that involves a state of cardiac standstill, with either asystole or agonal electrical activity, has a worse prognosis (69).

Fluid resuscitation of trauma patients with low blood pressure causes volume expansion and, consequently, revascularization of tissues and organs that were previously ischemic with reperfusion injury and interstitial edema (53, 71). Intravascular fluid escapes into the interstitial space during reperfusion and supplies high concentrations of the circulating substances in blood to the cells in this early posttraumatic period. In turn, an increase in cell membrane permeability secondary to the ischemia may favor the selective cellular supply of these substances (Fig. 2).

In addition, stress caused by the increased blood flow secondary to vasodilation may alter the endothelial cell redox state and lead to an increase in intracellular oxygen free radicals or reactive oxygen species (72, 73). In particular, high levels of oxidative stress result in the induction of vascular inflammatory genes via redox-sensitive signaling pathways and activation of redox-sensitive transcription factors (73). Therefore, oxidative stress may provide a molecular mechanism that links nervous or vasoactive functions with immune functions through the expression of a selective set of vascular inflammatory gene products, for example, cytokines, adhesion molecules, and enzymes (60).

David Cuthbertson first described two different phases, "ebb" and "flow," in the evolution of patients with severe injury (74). Clinically, the ebb phase is characterized by ashen facies, thready pulse, and cold clammy limbs (58, 74). In this phase, hemodynamic instability requires fluid resuscitation and patients present clinical edema (58). During deep shock and after resuscitation with isotonic fluid, the endothelial cells and red blood cells also swell. Therefore, administration of hypertonic saline can prevent at least some of this swelling, thus enhancing pulmonary and systemic microvascular perfusion (75, 76). Pentoxifylline associated with hypertonic saline improves the results still more, perhaps because it prevents both disturbed intracellular calcium (Ca^{2+}) regulation and oxygen free radical injury after hemorrhagic shock/resuscitation (77–80).

Because prolonged operative times are frequent in this phase, and because patients often suffer multiple injuries, such as abdominal visceral or vascular trauma, chest trauma, and open fractures, many such patients show progressive intraoperative physiology deterioration, typically manifested as acidosis, hypothermia, coagulopathy, and massive edema (81). This initial period, called hemodynamic instability by Hill and Hill (58), lasts about 3 days. When it is finished, patients present a positive fluid balance of about 4.7 liters and clinical edema.

If the intense accumulation of liquid in the interstitial space represents the regression of the organism to a stage in which cellular nutrition by diffusion predominates, it could be considered that the metabolic abnormalities that coexist, such as hypoxia, oxidative metabolism decrease, rapid depletion of adenosine triphosphate levels, and hypothermia (58, 71), are the appropriate ones to satisfy the limited energetic needs of this primitive type of nutrition (51). Thus, both the reabsorption of an excessive supply of liquid and substrates as well as the drainage of waste products derived from cellular metabolism would be done predominantly by the lymphatic vascular system.

If the resuscitation is adequate, the patient enters the flow phase, or the hypermetabolic phase, in which core temperature rises, cardiac output increases, and diuresis occurs (58, 74). In this flow, or warm-pink phase, the so-called immune response as a whole produces cellular and bacterial infiltration of the tissues and organs, which would be made up of transmigration of leukocytes through the venular endothelial cells, SIRS, and infection or sepsis (82–88). Adhesion molecules, together with chemokines, play an essential role in polymorphonuclear cell, monocyte, and lymphocyte tissue infiltration (88, 89).

Furthermore, the reduced blood flow and shear rate in postischemic tissues should promote blood cell–to–endothelial cell adhesion (90). Activation of NFκB in endothelial cells by low shear stress results in an increased expression of the VCAM-1, which in turn, mediates the increased adhesion of circulating monocytes (91).

Several laboratory and clinical studies have demonstrated the close relationship between trauma, shock, SIRS, and sepsis. These studies show that trauma and hemorrhagic shock may induce SIRS, which results in severe depression of immunologic functions, and leads to the development of multiple organ failure, severe sepsis, or septic shock (54, 83, 84, 92, 93).

The exaggerated inflammatory response to a second insult after the initial trauma has been explained according

to the "two-phase pattern" (94), or the "two-hit model" (95). The first event, or "hit," is the initial tissue trauma, shock, or both, which leads to generalized inflammation within hours of injury and appears to prime the immune system. The priming process itself can be relatively asymptomatic; however, with a second insult or hit, the host response produces relatively greater quantities of mediators, which then produce hemodynamic instability and tissue injury (84, 95, 96). If the second hit is only a modest infection or endotoxemia, an amplified generalized inflammatory response then develops (95, 97).

However, the establishment of late vasomotor disorders (septic shock) in a patient with polytrauma could also represent a mechanism of regression to an early nutritional state by diffusion. Under this supposition, the objective would be to increase endothelial permeability to the maximum to increase the interstitial liquid volume. Peripheral vasodilation with failure of the vascular smooth muscle to constrict would be an effective mechanism for doing this. Both of these are vascular motor alterations characteristic of vasodilatory shock (70), and even more of cardiorespiratory arrest.

In addition, because a primed cell has the ability to respond to a second stimulus in an altered way, which in turn can be an adaptive (constructive) response or a maladaptive (destructive) response (98), it may be considered that the response to a second stimulus can act, favoring the progression of the inflammatory response (beneficial), or, to the contrary, making it difficult due to interruption and consequent regression to its initial stages (harmful). Thus, the different intensity and duration of the vasomotor response in the tissues and organs of the traumatized patient could determine the sequence and severity of the evolution.

The mediators released during the immune phase of the systemic response to the injury, for example cytokines (99, 100) or acute-phase proteins (101), have a similar contrasting meaning; that is, immunostimulant and immunosuppressant (102). This would explain why a prolonged and excessive immunostimulant response may progress to further tissue injury, immunosuppression, and finally, to multiple organ failure and mortality (103).

Anti-inflammatory mechanisms are activated after trauma (93, 104), depending on the severity of injury (100), and acquired derangements of one or many of the immune antibacterial defenses are common after injury and can produce energy associated with a markedly increased incidence of sepsis and associated mortality (102, 105). Thus, two sets of mechanisms must be matched for host survival: ability to mount a rapid inflammatory response to injurious microbial invasion and ability to refrain from doing so otherwise (106).

Anticytokine trials in intensive care units have been carried out but with disappointing results. Interferon (IFN)-γ, soluble TNF receptor (sTNFr), IL-1 receptor antagonist (IL-1 Ra), TNF monoclonal antibody, antithrombin III, platelet-activating factor receptor antagonist (PAFra) bactericidal/permeability-increasing protein ($rBPI_{21}$), bradykinin antagonist, and activated protein C (93, 102, 107) stand out among the numerous potential immunomodulator therapies that have been investigated for patients with trauma and sepsis.

However, this immune phase of the inflammatory response could have other meanings. For example, Schwartz and Kipnis (108, 109) have demonstrated that the immune response against self-compounds residing in damaged tissues of the CNS confers protection against destructive self-compounds. Specifically, the ability to resist the consequences on CNS insults is T-cell dependent. According to these authors, the healthy CNS appears to be hostile to immune cells, and vice versa; the injured CNS, on the other hand, is immune friendly.

These results also make it possible to consider the hypothetical trophic and thus beneficial activity of the inflammatory cells that infiltrate the epithelial cells (intestine, liver, lung) in the traumatized patient during this inflammatory response phase (84). Under this supposition, infiltration by neutrophils and macrophages of the organs that have previously suffered ischemia-revascularization would lead to the arrival of cells with great digestive capacity and with trophic capacity for the neighboring cells.

Similar digestive and trophic functions could be performed by the bacteria and bacterial products that invade the organism by translocation from the intestine (54, 58, 71, 110). Furthermore, these functions of the inflammatory cells and intestinal bacteria would be performed in an environment that is still characterized by a deficient supply of oxygen as well as by the deficient capacity for its use.

Like another organ of the human body, the human gut flora is a complex association of cells that collectively perform essential functions (110). These bacteria break down complex food ingredients that cannot be digested by the enzymes of the gastrointestinal secretions and have the capacity of using proteins of the pancreatic juice and the apoptotic gastrointestinal mucosa cells, which are replaced every day as sources of fermentation (111). In addition, evidence suggests that the bacteria of the gastrointestinal tract consortium contribute to host nutrition by liberating and generating simplified carbohydrates, amino acids, and vitamins (110).

The digestive and trophic functions, which are both performed by the inflammatory cells as well as by the translocated intestinal bacteria, are the cause of a clinical state characterized by temperature greater than 38°C, and hypermetabolism during SIRS (84) is an attractive hypothesis. Coexistence of the inflammatory response of leukocytes, apoptotic cells, and bacteria from the intestine in this immune phase could permit such suspicion.

Sepsis may not be attributable only to an "immune system gene haywire" but may indicate an immune system that is severely compromised and unable to eradicate

pathogens (102). However, immunosuppression can also possess a trophic sense, because one of its mechanisms is the apoptosis and later phagocytosis of the inflammatory cells (Fig. 2; Ref. 88).

Another abnormality that seems to be characteristic in these phases of systemic inflammatory response is the prominence developed by the lymphatic vascular system in detriment to the blood vascular system. Thus, gut barrier failure may be involved in the pathogenesis of shock-induced distant organ injury via gut-derived factors; for example, cytokines from the gut-associated lymphoid tissue (GALT) carried in the mesenteric lymph rather than in the portal circulation (112). In addition, the primary route of bacterial translocation is via the mesenteric lymph. Thus, intestinal bacteria do not need to reach the portal circulation to induce a systemic inflammatory state (112, 113).

On the contrary, the blood vascular system seems to reduce its prominence in SIRS and sepsis, with a fall in systemic vascular resistance caused by vasodilation and a severe pulmonary shunting (84). In this way, a condition marked by failure of oxygen extraction, anaerobic metabolism, and excess lactate production is produced, although paradoxically, it coexists with hypermetabolism and fever (54, 57, 58, 84).

During the evolution of the nervous and immune phases of the inflammatory response, the organism suffers progressive deconstruction with depletion of the hydrocarbonate, lipidic, and protein content from its deposits (57, 58), as well as multiple or successive dysfunction and posterior failure or necrosis of the specialized epithelium, that is, the pulmonary (acute respiratory distress syndrome), gastrointestinal (changes in gastrointestinal barrier and bacterial translocation), hepatic (insufficiency and failure), and pancreatic (pancreatitis) ones (84).

Patients who die after a prolonged period of resuscitation and support in intensive care units can have very different initial diseases, but the final problem in each is multiple or total systems failure (114). It has been proposed that the host is destroying itself rather than being destroyed by bacteria (83).

However, the dysfunction or failure of the specialized epithelia of the body could also represent an accelerated process of epithelial dedifferentiation, favored by the implantation of a decrease in prominence both of the blood circulation as well as oxidative metabolism in the body.

Catabolism shows different patterns during the evolution of the systemic inflammatory response patterns. It is characterized by gluco-neogenesis, with increased glucose and lactate levels, lipolysis, and proteolysis in the initial response to multiple trauma (58, 115). This response rapidly provides the metabolic substrates to the tissues with post–ischemic-reperfusion increased endothelial permeability (nervous phase) and allows activation of the immune system with synthesis of mediators such as the cytokines or the acute-phase proteins (immune phase; Refs. 100, 101, 115).

The hypermetabolic state during SIRS is generally accompanied by protein catabolism, negative nitrogen balance, marked body weight loss, and anorexia (58, 84, 115), whereas peripheral anabolic pathways are inactivated (114). It has been argued that the usual postinflammation adjustments in body energy flux and body nitrogen are regulated components of a metabolic response to acute inflammation, which renders normally protected sources of endogenous energy and substrate available for repair and recovery during the convalescence period (116).

However, during prolonged critical illness, lean tissue is wasted despite feeding, a problem that often persists even after the underlying disease has resolved, thus perpetuating intensive care dependency (115). In this chronic phase of the critical illness, the wasting syndrome is associated with a neuroendocrine dysfunction characterized by hypothalamic rather than pituitary dysfunction (114, 116). A prolonged hypermetabolism period after surgery has been demonstrated. In patients with an orthotopic liver transplantation, restoration of protein stores occurs very slowly and incompletely, and only about half of the protein lost in the early postoperative phase is regained by 12 months. This continuing protein deficit has suggested the existence of persisting metabolic stress (117).

The hypothetical capacity of the organism to involute or dedifferentiate could represent a return to early stages of development. Therefore, it could form an effective defense mechanism against injury because it would make it possible to retrace a well-known route, that is, the prenatal specialization phase during the endocrine phase of the inflammatory response. This specialization would require the return of the prominence of oxidative metabolism, and thus angiogenesis in the affected epithelial organs to create the capillary bed that would make the regeneration of the specialized epithelial cells possible (Fig. 2).

However, this last phase of the systemic inflammatory response has the disadvantage that it develops its morpho-functional specialization in an extrauterine environment, without the functional support of the placenta. In this supposition, perhaps the popular saying "born again" applied to coming through a great danger unhurt (or survival of a serious injury) could have the mentioned physiopathological meaning here.

In addition, the specialization and maturation with remodeling of the tissues should be considered a slow process that is not exempt of complications.

In these long-term phases it has been found that approximately half of these patients suffer a posttraumatic stress disorder that can occur with neuroendocrine and immunological alterations (117). Because inclusion of these alterations in the general sense of the posttraumatic systemic inflammatory response would be of interest, it may be necessary to extend its "hospital" or health care concept.

If the symptoms and signs that are dependent on the vasomotor alterations, which are the main figures of

the initial phases of the inflammation, predominate in the descriptions of the local and systemic inflammatory responses made by Celsius and Cuthbertson, respectively, it is possible that a new conception of this important response of the body to the injury could facilitate the incorporation of the alterations that are characteristic of the later evolutionary phases into its definition.

In this case, a real integrating definition of the inflammatory response could be obtained. It would include both the initial or acute alterations as well as those that are produced in the longer period, which could be considered chronic. In addition, representation of the posttraumatic inflammatory response, such as an expression of the interrelated functional systems, could help to integrate the biochemical knowledge into the functional meaning that each system has during the clinical evolution of patients (15, 16, 118–120).

It is also tempting to suppose that the successive and different events that make up the posttraumatic inflammatory response represent a summary of the respective phases that have determined the evolution of the body or phylogeny. Under this supposition, the interpretation of the characteristics of each one of these phases would make it possible to reconstruct how life was in previous stages. Thus, according to the trophic sense of the inflammatory response, initial nutrition would be dominated by fluid, intermediate nutrition by inflammatory cells and lymphatic vessels and the last, which would be induced by the mature body, blood, and blood vessels.

In addition, after an anaerobic situation (ischemia), there would be a period of defective use of oxygen with production of reactive species of oxygen (ischemia-revascularization and activation of inflammatory cells), and finally, compartmentalization of oxygen would be produced for its specialized use by very differentiated cells in the blood capillaries.

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