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Metabolic Response to Severe Surgical Illness: Overview

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Abstract. Severe surgical illness results in metabolic responses that mobilize substrate (amino acids and fatty acids) from body stores to support vital organs, enhance resistance to infection, and ensure wound healing. Central to this process is the redistribution of body protein, which moves from skeletal muscle to support the central viscera. If unsupported, this protein-wasting state could result in prolonged convalescence, diminished immunity, and poor wound healing. Present evidence suggests that the central nervous system plays a major role in regulating this protein catabolic response. Infusing exceedingly small quantities of the proinflammatory cytokines into the brain can mimic injury responses, and central cytokine blockade may be one therapeutic approach to attenuating these responses safely in the future. Additional evidence also demonstrates that the function of the hypothalamus and anterior pituitary is dampened during the later stages of severe surgical illness, and the possibility of hormonal replacement therapy needs to be explored.

Injury and infection/inflammation are the bases for most severe surgical illness. Metabolic changes following these events result in the increased mobilization and utilization of substrate: fatty acids, amino acids, and glucose. These substances or their precursors arise primarily from tissue in the carcass (skeletal muscle and adipose tissue), and this abundance of substrate is provided to ensure the function of essential visceral organs, supply building blocks for tissue repair, and support an upregulated and expanding immunologic system. This sequence of events that redistributes substrate from the carcass to visceral organs is initiated and mediated by alterations in the hormonal environment and, directly or indirectly, by signals elaborated by the inflammatory process (cytokines and other mediators). Complete or partial starvation, immobilization, regional ischemia, acidosis, some therapeutic interventions, and other *systemic factors* support and amplify these catabolic changes. Exceedingly powerful *local factors* mediate proliferation of immunologic cells and signal for repair at the site of injury or infection, both highly anabolic processes.

The metabolic response, which has evolved to enhance survival, provides a mechanism to resolve our own biologic problems created by tissue injury or inflammation. We feed ourselves, mobilizing energy from stored body fat and deriving amino acids from our lean body mass. The latter nitrogen-containing substrates are used as building blocks for new protein (both tissue and acute-phase proteins) and provide precursors for gluconeogenesis and antioxidant defenses. Fat is a stored fuel source readily utilizable for such purposes, but the amino acids arise primarily from skeletal muscle protein, limiting efficient locomotive function, which is no longer an immediate priority in the acutely ill individual.

This indelible metabolic response program allows for the injury to heal or the inflammatory process to resolve. If these events do not occur, we succumb to the primary insult, an occurrence frequently observed before the evolution of modern-day intensive care. With survival and resolution of the acute events, the individual undergoes a period of *convalescent anabolism,* which restores fat stores and protein-containing lean tissue.

Enter the miracles of modern medicine and contemporary intensive care. Through our therapeutic interventions, we can now resolve many of the problems our body is programmed to solve. We can alter pain perception, modify inflammation, stimulate skeletal muscle anabolism, provide an abundance of substrate (by forced enteral feedings or intravenous infusion of nutrients), create states of hyperoxia, correct acid–base disturbances, and alter mentation, to just name a few therapeutic maneuvers performed in an intensive care unit (ICU). As a result, modern therapy is often at odds with our indelible metabolic program created through evolutionary forces to enhance survival. The tensions caused by our modern medical practice and our innate metabolic program are frequently associated with a variety of iatrogenic complications observed in ICU patients. For example, the injury response results in insulin resistance and mild hyperglycemia: Is it any wonder that patients frequently develop clinically significant hyperglycemia and fatty liver infiltration with the infusion of large amounts of hypertonic glucose-containing nutritional solutions?

How do we resolve these conflicts between modern intensive care and our innate metabolic responses? A conservative approach would be to allow the body to respond to the stresses of severe surgical illness (e.g., following severe burns, fecal peritonitis, multiple trauma) without major metabolic intervention and assume that the evolutionary program would provide for a successful recovery. Although this approach is acceptable in the previously healthy patient undergoing an elective operative procedure without complications, it nevertheless is retrogressive in patients with severe critical illness. Such a treatment course would result in severe wasting and prolonged convalescence, and it is frequently associated with late deaths due to infection. In individuals with severe surgical illness, the mortality rate has significantly decreased because of our new medical knowledge and the in-

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Table 1. Response components.

Clinical manifestations
Fever
Tachycardia
Tachypnea
Presence of a wound or inflammation
Anorexia
Laboratory changes
Leukocytosis/leukopenia
Hyperglycemia
Elevated C-reactive protein/altered acute-phase reactants
Hepatic/renal dysfunction
Metabolic manifestations
Hypermetabolism
Accelerated gluconeogenesis
Enhanced protein breakdown
Increased fat oxidation
Physiologic consequences
Increased cardiac output
Increased ventilation (e.g., gas exchange)
Increased membrane transport
Weight loss; if prolonged contributes to prolonged convalescence
Wound healing

creased capacity for enhanced metabolic support. However, treatment-associated complications are still all too frequent, and convalescence and return to normal function after a severe catabolic illness remains prolonged. We must now develop new hypotheses that can be tested that incorporate new metabolic approaches in an attempt to improve the care and recovery of critically ill surgical patients. We must be able to minimize the adverse posttraumatic events while maintaining the recuperative components of the responses that facilitate wound healing, tissue repair, resistance to infection, and convalescent recovery.

Response Components

Although the surgeon rarely needs to be concerned with components of the metabolic response following mild to moderate injury or infection in uncomplicated surgical patients, these responses predominate in patients admitted to the burn and trauma service or to the surgical ICU. The response components are categorized on Table 1. The clinical and laboratory manifestations of injury responses are common variables that are frequently monitored because they reflect the clinical condition of the patient. The metabolic manifestations require more specialized approaches for study, and this methodology has been discussed in more detail elsewhere [1]. The physiologic consequences of these responses serve as the basis for modern intensive care: support of adequate cardiac output, optimization of ventilation often using a mechanical ventilator, monitoring fluid balance and organ function, and providing adequate nutrition.

All of these events occur while the wound is healing or the inflammation is resolving. These endpoints are usually achieved unless the patient has associated diseases that interfere with wound vascularization or inflammation, the individual is malnourished, or an intervening complication occurs. With mild to moderate injury, this catabolic response causes minimal debility; with the more extensive injuries and/or infections, utilization of body protein may prolong convalescence and even contribute to mortality.

Table 2. Alterations in rates of protein synthesis and catabolism that may affect hospitalized patients.

	Synthesis	Catabolism
Normal		
Starvation	↓	0
Fed, bed rest	↓	0
Elective surgical procedure	↓	0
Injury/sepsis		
Intravenous dextrose	↑ ↑	↑ ↑ ↑
Fed	↑ ↑ ↑	↑ ↑ ↑

↓: decrease; ↑: increase; 0: no change.

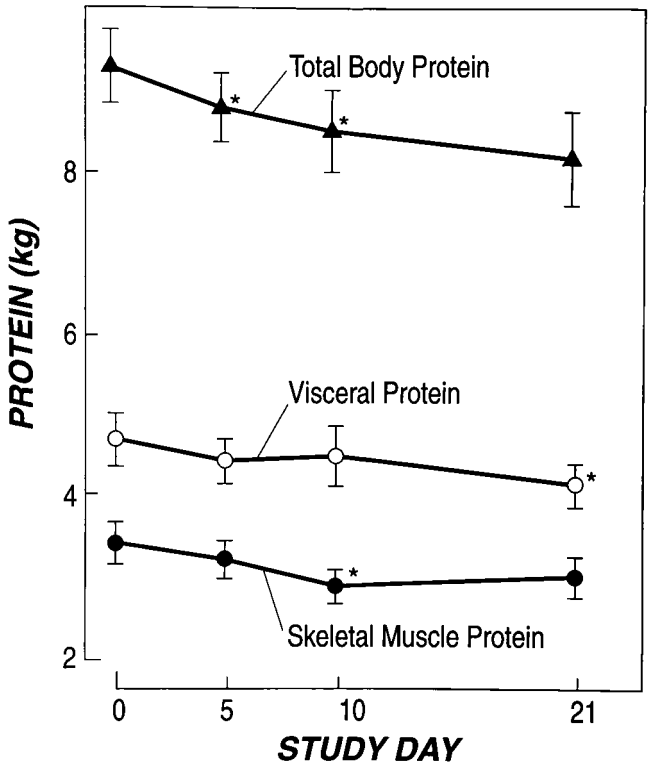

Fig. 1. Following severe peritonitis and operation there is a progressive fall in total body protein, skeletal muscle protein, and finally visceral protein despite "adequate" nutritional support. Results are means ± SEM. *Significant ($p < 0.05$) change from the preceding measurement. (Adapted from Plank et al. [12], with permission.)

Protein Redistribution and Accelerated Nitrogen Loss: Central Features of the Catabolic Response

Normal body composition is usually divided between four compartments: adipose tissue, minerals (primarily bone), water, and protein. The absolute size of these compartments and relation between them depends on the age, weight, disease state, and nutritional status of the patient. Protein represents the active functioning tissue of the body that contributes to structure (skeletal muscle) and function (enzymes).

The protein content of the body can be regionalized by considering the protein distributed in skeletal muscle and that found in visceral organs. This concept is important because following se-

Table 3. Effects of varying the TNF signal on the host response.

Dose of TNF infused ($\mu g/m^2$)	Response	Clinical correlate
1	Hypoferremia	Subclinical infection
	Myalgia and headache	—
	Anorexia	Influenza
20	Fever	Acute appendicitis
	Tachycardia	—
	Elevated acute-phase protein levels	—
	Rigors	—
	Elevated stress hormone levels	Intraabdominal abscess
> 500	Fluid retention	Major thermal injury
	Lymphopenia	—
	Hypotension	—
> 620	Decreased conscious level	Septicemia
	Profound hypotension	Severe acute pancreatitis
	Pulmonary edema	Infected massive burns
	Oliguria	—

TNF: tumor necrosis factor.

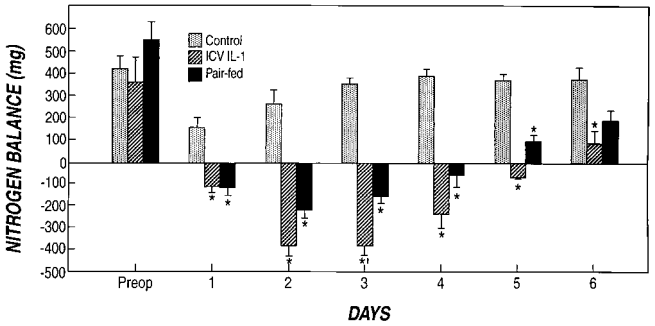

Fig. 2. Nitrogen balance in control rats and animals infused with intracerebroventricular (ICV) interleukin-1 (IL-1) and their pair-fed control. Although some of the nitrogen loss could be attributed to decreased food intake, the ICV-infused animals demonstrated increased protein catabolism compared with pair-fed controls. Results are means ± SEM. $^{*}p < 0.05$ vs. control; $^{\dagger}p < 0.05$ vs. pair-fed. (From Hill et al. [16], with permission.)

vere surgical illness there is active transfer of amino nitrogen from skeletal muscle to visceral tissues. Skeletal muscle mass represents 30% to 50% of total body protein, is greater in men than women, and declines with age. Between ages 20 and 80, the total muscle cross-sectional area declines about 40% [2]. These changes affect strength and endurance with aging, although some of these events can be reversed with exercise. In the context of injury responses, the quantity of muscle mass present in a patient at the onset of illness may determine his or her long-term ability to withstand a catabolic disease. This is one of the reasons elderly patients, with their reduced skeletal muscle mass, are so vulnerable during catabolic illness and require prolonged mechanical ventilation and periods of long-term recovery and rehabilitation [3].

Following an operation or injury, the increased urinary excretion of nitrogen from the body is roughly related to the extent of the injury. The nitrogen is primary lost in the form of urea, which represents about 85% of the urinary nitrogen loss, although this proportion varies widely. Creatinine, ammonia, uric acid, and amino acids are also found in the urine in larger quantities than normal. The nitrogen molecule is used as a surrogate marker of protein because of the fixed relation between the two substances (e.g., protein in grams/6.25 = nitrogen in grams).

Thus, the net loss or gain of body protein is determined by nitrogen balance, and this is a general measure of the catabolic state of the patient. Yet maintenance of protein within an individual tissue is a balance between the protein synthesis and breakdown of that particular organ. Synthesis and breakdown are often mismatched during catabolic states, resulting in organ protein loss or gain. The catabolic response occurs by one of two mechanisms: synthesis decreases but breakdown continues in a normal manner, or synthesis remains the same and breakdown is increased (Table 2).

As individual tissues lose or gain protein, there is uptake or release of amino acids into their specific regional vascular beds. Moreover, there appears to be coordinated movement of amino acids among organs, with release of these substances from the carcass and uptake by visceral organs. During the acute phase of injury, amino acids are released from noninjured extremities of injured patients [4]. Because skeletal muscle represents the major protein-containing tissue in the extremity, this increased release in amino acids documents the accelerated net skeletal muscle proteolysis that occurs as a characteristic catabolic response to injury. Additional studies have shown that amino acids are avidly extracted from the bloodstream of the splanchnic bed [5]. In large part it is represented by extraction of amino acids by the liver for the synthesis of structural, plasma, and acute-phase proteins. In addition, ureagenesis is accelerated, and the urea is eventually excreted in the urine, thereby accounting for the increased posttraumatic nitrogen excretion.

These observations are consistent with other studies of tissue protein synthesis rates following isotropic infusions into "stressed" animals. Taken together with the human studies these investigations confirm that protein turnover responds to injury and infection in a manner that redistributes body protein to satisfy the body's needs. The synthesis rate is decreased in "nonessential" tissues (e.g., limb skeletal muscle or gut) and is maintained or enhanced in tissues where work is increased (respiratory and cardiac muscle, lung, liver, spleen). Data generally support the hypothesis that serious surgical illness stimulates enhanced protein turnover. These events result in translocation of protein from skeletal muscle to the visceral organs (primarily liver, spleen, and heart) that are vital for survival. Additional nitrogen is processed as waste and converted to urea for excretion.

Two amino acids, alanine and glutamine, account for approximately 50% to 75% of the amino acid nitrogen released from skeletal muscle [6]. Alanine is an important glucose precursor and indirectly provides this fuel source, which is essential for several key tissues; glutamine is a gluconeogenesis substrate as well but also serves as primary substrate for immune cells and enterocytes, participates in acid–base homeostasis, and serves as a precursor for glutathione (an important intracellular antioxidant).

It has been hypothesized that the tissue requirements for glutamine may outstrip the ability for tissue (particularly skeletal muscle) to produce this amino acid. Hence a relative deficiency state exits [7] characterized by a fall in glutamine concentrations in both the plasma and tissue compartments. The provision of exogenous glutamine in these stress situations when inflammation

persists has been shown to correct plasma and tissue stores, improve the nitrogen balance, and often reduce morbidity and mortality [8–10]. Thus glutamine has been considered a conditional essential amino acid, the conditions being the presence of inflammation or injury (or both), which increases the glutamine demand.

The liver performs multiple functions following injury, but one unique role is to alter dramatically the plasma concentration of certain circulating proteins called "acute-phase" reactants. These proteins may be present in the bloodstream during normal conditions, but their concentrations change rapidly owing to the sudden increase or decrease in hepatic synthesis of these secretory substances [11]. The signals for these synthetic changes include elaboration of glucocorticoids, interleukin-6 (IL-6), other cytokines, and possibly nervous signals arising from the brain. It is speculated that the acute-phase proteins contribute to host defense mechanisms.

What are the clinical consequences of this increased net protein catabolism that follows injury and infection? In the short term, a well nourished individual sustains minimal debility because of the negative nitrogen balance that accompanies an elective operative procedure. In the long term, the response may be more deleterious. For example, Plank and associates studied a group of seriously ill patients with peritonitis [12]. Body compositional studies revealed that patients lost a total of 1.5 kg body protein over the first 3 weeks of their illness, despite "adequate" nutritional support (Fig. 1). Initially this deficit occurred in skeletal muscle, and such losses can manifest as decreased respiratory muscle function, decreased strength and activity, and prolonged convalescence. Research is needed to evaluate a variety of treatments that can be used to attenuate or reverse the protein catabolic response to injury.

Wound Signals: How Do We Know When There Is an Injury?

Since the early descriptions of injury responses during the 1930s, interest has been directed toward identifying those factors that mediate the metabolic and physiologic alterations. The response mediators can be divided into two general categories: afferent nervous signals and circulating signals. Although these signaling systems affect a variety of organ systems, their major impact appears to be on the central nervous system, which then integrates this information. Interaction between nervous and circulating signals have only recently been recognized.

Afferent Nervous Stimuli

The most rapid communication between an injured area and the brain is via the afferent nervous system. With injury, we feel pain, which sets into motion the complex array of injury responses. Hume and Egdahl injured the distal extremity of an animal before and after denervating the hind limb [13]. When the peripheral nervous system was intact, there was a brisk pituitary-adrenal response; following nerve transection, the response did not occur. Such nociceptive pain signals are transmitted primarily by small myelinated (A delta) and small unmyelinated (C) sensory afferent fibers to the dorsal horn of the spinal cord. Subsequently, these impulses are transferred cephalad to the ventral-posterior nucleus of the thalamus.

Modern clinical practice often modifies these signals and therefore alters the stress response; the use of spinal and epidural anesthesia is a useful technique for interrupting this afferent nervous pathway. When operations are performed on the lower extremities or in the lower abdomen, spinal blockade greatly attenuates the stress response (e.g., reduces stimulation of the pituitary-adrenal axis) and possibly shortens the postoperative convalescence period [14].

Circulating Factors

Studies in patients undergoing operations in denervated extremities have demonstrated that changes still occur in acute-phase protein concentrations, fever, granulocytosis, and the coagulation cascade. These responses appear to be initiated and propagated by a variety of factors arising from the wound, including complement products, arachidonic acid metabolites, platelet-activating factor, cytokines, and other substances. Initially, the signals may serve locally to enhance wound healing; and as the severity of injury increases, these substances may diffuse into the bloodstream to then affect other tissues and organs, such as the brain, bone marrow, and liver.

Cytokines have attracted much attention in recent years and these proinflammatory factors [IL-1, tumor necrosis factor (TNF), IL-6, IL-8, and interferon to name a few] may play a causal role in effecting some of the responses that occur. These mediators primarily act locally and exert effects on immunologic cells and tissue repair. However, if these factors reach the bloodstream, systemic responses are observed. Infusion of IL-1 or TNF elicits fever, alterations in glucose metabolism, negative nitrogen balance, and hepatic acute-phase synthesis (Table 3). IL-6 may also elicit some of these events. The actions of these cytokines may be due to the direct effects of the agent on a specific tissue; or in the case of TNF, the effects may be secondary through stimulation of the brain and elaboration of counterregulatory hormones, glucagon, cortisol, and catcholemines.

These inflammatory factors are not consistently detected in the bloodstream (the single exception being IL-6), and blocking studies using systemically administered monoclonal antibodies and modulating one specific mediator have not consistently attenuated all of these metabolic responses. The exact pathway and humeral substance that signals the central nervous system from the site of inflammation remains uncertain at this time.

Role of the Central Nervous System (CNS)

The brain is responsible for integrating both the nervous and humeral signals it receives. The primary site for these responses to be integrated is the hypothalamus; removing the brain above this level in experimental animals does not affect the pituitary-adrenal response to stress. The brain stem is necessary for trauma responses, however, as administering large doses of opiates to injured patients greatly dampens hypothalamic function and significantly reduces oxygen consumption, heart rate, core temperature, and minute ventilation.

Following integration of afferent signals, the hypothalamus has two major effector arms that are used to regulate physiologic responses. The first is the sympathoadrenal-medullary axis and

Table 4. Effect of CNS blockade of IL-1 on the metabolic effects of IL-1.

Treatment group[a]	Saline/saline	Saline/IL-1	IL-1ra/IL-1
No.	10	5	5
Cumulative chow intake (g)	114 ± 10	70 ± 10*,**	101 ± 8
Weight change (g)	4 ± 8	−30 ± 2*	6 ± 6
Cumulative nitrogen balance (g)	1913 ± 201	163 ± 123*,**	1325 ± 212
Total body nitrogen (g)	7.36 ± 0.29	6.33 ± 0.12*,**	7.60 ± 0.28
WBC ($10^3/\mu$l)	11.3 ± 1.1	31.6 ± 8.41*,**	24.4 ± 2.9*
Iron (mg/dl)	186 ± 21	87 ± 17*,**	176 ± 33
Albumin (g/dl)	3.44 ± 0.11	3.00 ± 0.05	3.09 ± 0.08

Results are means ± SEM.

CNS: central nervous system; IL-1: interleukin-1; IL-1ra: interleukin-1 receptor antagonist; WBC: white blood cell count.

[a]Each animal was implanted with two osmotic pumps, one infusing the lateral cerebral ventricle and the other subcutaneous tissue. The first treatment listed represents the substance infused into the CNS, the second treatment is the infusion into the subcutaneous tissue. Thus, saline/IL-1 is saline into the CNS and IL-1 into subcutaneous tissue.

*$p < 0.05$ vs. saline/saline; **$p < 0.05$ vs. IL1-ra/IL-1.

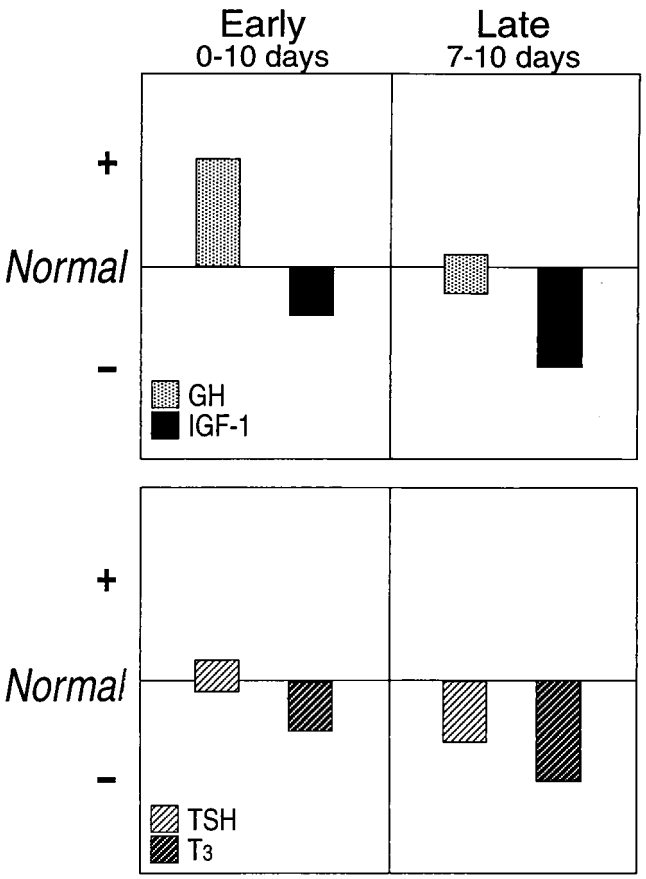

Fig. 3. Relation between two anterior pituitary hormones [growth hormone (GH) and thyroid stimulating hormone (TSH)] and the secondary signals [insulin-like growth factor-1 (IGF-1) and triiodothyronine (T_3)]. Under normal conditions, low concentrations of IGF-1 and T_3 would result in increased levels of GH and TSH. This negative feedback relation appears disturbed, especially in the later stages of illness. +: increased above normal; –: below normal. (Adapted from G. Van Der Berghe et al. [22] with permission of the author. © The Endocrine Society.)

the second is the hypothalamic-pituitary-adrenal (HPA) axis. Activation and modulation through both systems serve to mediate in large part the stress response to critical illness.

One area of CNS regulation only recently recognized is the role cytokines may play in influencing brain function during inflammatory states. Astrocytes and microglia have been shown to express several cytokines and cytokine receptors, and they increase cytokine release following a variety of stimuli such as administration of lipopolysaccharide (LPS) or exposure to a hypoxic environment. Acute injection of IL-1 or IL-6 into the lateral ventricle of the brain or into specific areas of the brain have been shown transiently to cause pyrexia, anorexia, an adrenocortical activation, similar to responses observed following injury [15]. In a chronic infusion model [16] intracerebroventricular administration of IL-1, but not equal molar amounts of IL-6, caused anorexia, negative nitrogen balance, and weight loss (Fig. 2). These responses were not attenuated by clamping glucocorticoids at low concentrations via adrenalectomy and corticosterone pellet replacement.

Additional studies administered IL-1 subcutaneously into experimental animals and blocked the CNS effects by intraventricular infusion of an IL-1 receptor antagonist (IL-1ra) [17]. Central blockade significantly attenuated the protein catabolism that occurred with systemic IL-1 but only slightly affected the leukocytosis (Table 4). In similar studies, LPS was given as the provocative stimulus to rodents, and it increased glucose production [18]. When IL-1ra was infused into the CNS and the experiments were repeated, the gluconeogenic response was greatly attenuated. Thus the brain appears to modify and amplify certain components of the stress response through the actions of cytokines working within the CNS.

Cytokines are large lipophobic molecules and do not have ready access to the CNS, although they may circulate in the bloodstream and be actively transported into specific regions of the brain. Alternatively, cytokines may penetrate specific areas of the blood–brain barrier at one or more of the circumventricular organs. The vascular endothelium may act as a transducer for cytokines and generate other messengers that stimulate brain pathways. Alternatively, cytokines may damage the integrity of the vascular endothelium (or the blood–brain barrier), enter the brain, and stimulate central neural circuits. Finally, cytokines may stimulate peripheral neural pathways (e.g., the vagus) to send afferent signals to the CNS.

Increasing evidence has suggested that vagal pathways are utilized as the communication link between the peritoneal cavity and

the CNS, especially during episodes of intraabdominal infection. It has been shown that many CNS effects induced by intraperitoneal administration of LPS or IL-1 (e.g., fever, increased elaboration of ACTH, induction of the IL-1 message within the brain) can be blocked or attenuated by subdiaphragmatic vagotomy [19, 20]. Receptors appear to be present within the peritoneal cavity, as increased electrical activity has been observed in the vagus following intraportal injection of IL-1β [21]; and IL-1 receptors have been identified on abdominal paraganglia. These findings suggest that cytokines may be somewhat compartmentalized throughout the body and communicate with the brain via the vagus and other afferent nerves.

Has Modern Intensive Care Created a New Metabolic Disease?

Our biologic program was designed to provide for survival or death following injury or infection. Historically, recovery occurred over a rather short time, followed by convalescence and a more gradual return to full function. If recovery was not forthcoming, death occurred. This rather clear-cut selection process has changed with the development of modern intensive care. Respiratory failure, probably the most common cause of death, is now prevented with the use of mechanical ventilation. In addition, critically ill patients are frequently resuscitated if cardiac arrest occurs; renal failure is treated by dialysis; and gut failure is modulated by administration of parenteral nutrition. Thus the time scale for the programmed metabolic response endpoints (survival or death) had changed dramatically.

What is the consequence of this frameshift? Some have argued that a new iatrogenic metabolic state has been created. A previously unknown condition has been observed following a prolonged stay in the ICU: nonspecific and prolonged wasting of body protein that occurs in the face of providing adequate quantities of energy and protein. This process is often accompanied by the accretion of body fat in the presence of hyerpglycemia, insulin resistance, extracellular water and salt accumulation, hypokalemia, and hypoproteinemia. Others have argued that it is this environment of prolonged care in the ICU that allows the development of multiple organ failure.

Van den Berghe and colleagues have forwarded the hypothesis that there is an endocrinologic basis for these *later* changes ("later" is defined as 10 days or more following the onset of the critical illness), and that failure of protein anabolism in the later stages of critical care may reside in subacute or chronic attenuation of secretion of key hormones from the anterior pituitary gland, which delays the anabolism essential to recovery [22]. Moreover, the ability of these key pituitary hormones to stimulate their target organ hormones was also greatly attenuated during this later period of the catabolic response. For example, the anabolic effects of growth hormone (GH) are mediated via the production of insulin-like growth factor-1 (IFG-1); and the effects of thyroid-stimulating hormone (TSH) are mediated via the thyroid gland with the release of triiodothyronine (T_3) and thyroxine (T_4.) Van den Berghe et al carried out a series of detailed studies determining hormonal secretion rates in critically ill patients. When response patterns of these target hormones were examined, there was an inappropriately low secretory rate of the target hormone, even in the face of normal or near-normal pituitary hormonal concentrations. Despite these near-normal concentrations of GH and TSH, the IGF-1, T_3 and T_4 concentrations were quite low (Fig. 3). Because these hormones are vital to anabolism, protein synthesis, and recovery, it is hypothesized that administration of these factors would be of benefit during this *later stage* of critical surgical illness. Trials are now underway to test this hypothesis.

Résumé

L'agression chirurgicale, «sévère», engendre des réponses métaboliques qui mobilisent des substances stockées dans le corps (acides aminés et gras) pour être utilisées dans le soutien des organes vitaux, de façon à augmenter la résistance à l'infection et à garantir la cicatrisation. Au centre de ce processus se trouve la redistribution des protéines du corps aux organes principaux à partir du muscle squelettique. En l'absence d'apport nutritionnel, cette perte protéique pourrait être responsable d'une période de convalescence prolongée, d'une immunité diminuée et d'un défaut de cicatrisation. L'évidence à présent suggère que le système nerveux central joue un rôle majeur dans la régulation de cette réponse protéinique catabolique. Par l'infusion de petites quantités de cytokines pro-inflammatoires dans le cerveau, on pourrait stimuler des réponses lésionnelles. Le blocage entéral des cytokines pourrait être une des approches thérapeutiques pour atténuer ces réponses dans l'avenir. Il semble exister d'autres preuves qui démontrent que la fonction de l'hypothalamus et de l'hypophyse antérieure est entravée dans les stades tardifs de la maladie (agression) chirurgicale et la possibilité d'une thérapeutique de remplacement hormonal doit être explorée.

Resumen

La enfermedad quirúrgica grave resulta en la movilización de sustratos (aminoácidos y ácidos grasos) a partir de las reservas corporales para dar soporte al funcionamiento de órganos vitales, incrementar los mecanismos de defensa y asegurar cicatrización. Un aspecto central de este proceso es la redistribución de la proteína corporal, mediante su movimiento del músculo esquelético hacia las visceras centrales. En ausencia de soporte adecuado, tal estado de degradación proteica puede significar una convalescencia prolongada, inhibición de la inmunidad y cicatrización deficiente. La evidencia actualmente disponible sugiere que el sistema nervioso central juega un rol principal en la regulación de esta respuesta catabólica. La infusión de pequeñísimas cantidades de citocinas proinflamatorias en el cerebro puede simular las respuestas al trauma, y el bloqueo central de citocinas puede ser un futuro aproche terapéutico orientado a atenuar la magnitud de estas respuestas. Evidencia adicional también demuestra que la función del hipotálamo y de la hipófisis anterior resulta disminuida en las etapas avanzadas de la enfermedad quirúrgica severa, por lo cual merece explorarse la posibilidad del reemplazo hormonal.

References

1. Cooper, G.J., Dudley, H.A.F., Gann, D.S., Little, R.A., and Maynard, R.L.: Scientific Foundations of Trauma. Oxford, Butterworth Heineman, 1997, pp. 459–756
2. Lexell, J., Taylor, C.C., and Sjostrom, M.: What the cause of ongoing atrophy: total number, size and proportion of different fiber types

studied in whole vastus lateralis muscle from 15 to 83 year-old men. J. Neurol. Sci. *84*:275, 1988
3. Windsor, J.A., and Hill, G.L.: Weight loss and physiological impairment: a basic indicator of surgical risk. Ann. Surg. *207*:290, 1988
4. Aulick, L.H., and Wilmore, D.W.: Increased peripheral amino acid release following burn injury. Surgery *85*:560, 1979
5. Wilmore, D.W., Goodwin, C.W., Aulick, L.H., Powanda, M.C., Mason, A.D., Jr., and Pruitt, B.A., Jr.: Effect of injury and infection on visceral metabolism and circulation. Ann. Surg. *192*:491, 1980
6. Muhlbacher, F., Kapadia, C.R., Colpoys, M.F., Smith, R.J., and Wilmore, D.W.: Effects of glucocorticoids on glutamine metabolism in skeletal muscle. Am. J. Physiol. *247*:E75, 1984
7. Lacey, J.M., and Wilmore, D.W.: Is glutamine a conditionally essential amino acid? Nutr. Rev. *48*:297, 1990
8. Morlion, B.J., Stehle, P., Wachtler, P., Siedhoff, H-P., Köller, M., Köning, W., Fürst, P., and Puchstein, C.: Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. Ann. Surg. *227*:302, 1998
9. Griffiths, R.D., Jones, C., and Palmer, T.E.: Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition *13*:295, 1997
10. Hoodijk, A.P.J., Rijnsburger, E.R., Jansen, J., Wesdorp, R.I.C., Weiss, J.K., McCamish, M.A., Teerlink, T., Meuwissen, S.A.G.M., Haarman, H.J.T.M., Thijs, L.G., and van Leeuwen, P.A.M.: Randomized trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet *352*:772, 1998
11. Kushner, I.: The phenomenon of the acute phase response. Ann. N.Y. Acad. Sci. *389*:39, 1982
12. Plank, L.D., Connolly, A.B., and Hill, G.L.: Sequential changes in severely septic patients during the first 23 days after the onset of peritonitis. Ann. Surg. *228*:146, 1998
13. Hume, D.M., and Egdahl, H.: The importance of the brain in the endocrine response to injury. Ann. Surg. *150*:697, 1959
14. Christensen, T., Stage, J.G., Galbo, H., Christensen, N.J., and Kehlet, H.: Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. Surgery *105*:46, 1989
15. Barbanel, G., Ixart, G., Szafarczyk, A., Malaval, F., and Assenmacher, I.: Intrahypothalmic infusion of interleukin 1-β increases the release of corticotropin-releasing hormone (CRH) and adrenocorticotropin hormone (ACTH) in free moving rats bearing a push-pull cannula in the median eminence. Brain Res. *516*:31, 1990
16. Hill, A.G., Jacobson, L., Gonzalez, J., Rounds, J., Majzoub, J.A., and Wilmore, D.W.: Chronic central nervous system exposure to interleukin-1β causes catabolism in the rat. Am. J. Physiol. *271*:R1142, 1996
17. Hill, A.G.: Metabolic effects of proinflammatory cytokines. Thesis (Doctor of Medicine), University of Auckland, 1994, pp. 83–91
18. Lang, C.H., Cooney, R., and Vary, T.C.: Central interleukin-1 partially mediates endotoxin-induced changes in glucose metabolism. Am. J. Physiol. *271*:E309, 1996
19. Watkins, L.R., Goehler, L.E., Relton, J.K., Tartaglia, N., Silbert, L., Martin, D., and Maier, S.F.: Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci. Lett. *183*:27, 1995
20. Kapcala, L.P., He, J.R., Gao, Y., Pieper, J.O., and DeToall, L.J.: Subdiaphragmatic vagotomy inhibits intra-abdominal interleukin-1β stimulation of adrenocorticotropin secretion. Brain Res. *728*:247, 1996
21. Niijima, A.: The afferent discharges from sensors for interleukin 1-β in the hepatoportal system in the anesthesized rat. J. Auton. Nerv. Syst. *61*:287, 1996
22. Van den Berghe, G., de Zegher, F., and Bouillon, R.: Acute and prolonged critical illness as different neuroendocrine paradigms. J. Clin. Endocrinol. Metab. *83*:1827, 1998