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'New strategies for manipulating the metabolic response to severe illness'**

Modulating the metabolic response to injury and infection

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The host metabolic response to injury, be it defined as traumatic or infectious in nature, is characterized by diverse alterations in substrate turnover at the systemic and tissue levels (Lowry, 1986; Goldstein & Elwyn, 1989). Numerous studies attest to the extent of altered metabolic processes in injured and septic patient populations. For example, the isotopically determined rates of turnover for glucose, free fatty acids and of leucine emanating from the collaborative studies of Shaw and Wolfe (Shaw *et al.* 1985; Shaw & Wolfe, 1987; Wolfe *et al.* 1987; Jahoor *et al.* 1989) are presented in Table 1. Although a consensus of similar studies by other investigators notes a generalized increase in substrate turnover during the flow phase, such metabolic changes are dynamic in nature. Therefore, attention to the timing of such determinations in relation to the injury event as well as the severity and antecedent clinical management of the process is required.

Table 1. *Isotopically determined rates of substrate turnover in normal and severely injured or septic humans*

(Mean values with their standard errors)

	Energy expenditure (estimated as % of basal)	Turnover rate					
		Glucose (μmol/kg per min)		FFA (μmol/kg per min)		Leucine (μmol/kg per min)	
		Mean	SE	Mean	SE	Mean	SE
Normal	100	12.4	1.1*	6.7	0.3*	2.78	0.16§
Sepsis	120-130	25.0	1.8†	13.1	3.0‡	4.08	0.22§
Burns	>120	28.8	4.8*	14.5	1.1*	5.15	0.24§

* Wolfe *et al.* (1987).

† Shaw *et al.* (1985).

‡ Shaw & Wolfe (1987).

§ Jahoor *et al.* (1989).

It is also increasingly evident that such metabolic responses belie any simple mechanistic interpretation. It has been argued that much of the observed metabolic profile of the injured patient can be explained by excessive activity of one or more components of the classical stress-hormone response (Bessey *et al.* 1984; Gelfand *et al.* 1984). While the critically ill patient exhibits repeated or sustained levels of many such neuro-humoral components, the extent to which such hormones, either individually or in combination, initiate or sustain the observed metabolic responses remains uncertain (Lowry, 1986).

Previous clinical studies have sought to dissect the contribution of classical neuro-humoral stress-hormone components to post-injury hypermetabolism and substrate turnover. The kinetics of body protein metabolism have been widely studied during the acute post-injury phase. The regulation of the synthetic and catabolic components of protein metabolism appear to be sensitive to the phase of injury and, by implication, to the hormonal milieu. Although some have reported that increased adrenergic stimulation may acutely alter the oxidative and synthetic components of protein metabolism, we (Fong *et al.* 1991) and others (Matthews *et al.* 1990) have been unable to confirm any sustained influence of catecholamines on body protein kinetics in the absence of overt injury. When assessed in injured humans, selective adrenergic blockade suggests that the rate of net protein catabolism is modestly decreased after α -adrenergic blockade without an attendant influence on rates of glucose production (Shaw *et al.* 1988). Nevertheless, efforts to duplicate this hormonal milieu by exogenous infusions (Beaufriere *et al.* 1989; Fong *et al.* 1991) or alternatively at blockade of selected components of the neuro-humoral response in normal subjects (Kraenzlin *et al.* 1989) suggest that excessive adrenergic stimulation is insufficient *per se* to fully explain the metabolic consequences of severe injury or infection.

By contrast to the apparent lack of significant adrenergic influence on injury associated protein kinetics, a sustained period of hypercortisolaemia induces alterations in protein metabolism consistent with the observed clinical scenario (Beaufriere *et al.* 1989). While enhanced cortisol secretion may be contributory to the net protein catabolism of injury, studies of excess cortisol background in normal subjects fail to reproduce the magnitude of nitrogen wasting commonly observed after major injury (Bessey *et al.* 1984; Gelfand *et al.* 1984). Indeed, other components of the stress-hormone response, such as elevated growth hormone, may serve to attenuate the catabolic influences of glucocorticoids (Horber & Haymond, 1990).

INFLAMMATORY MEDIATORS

Additional classes of endogenous mediators also appear capable of influencing systemic and cellular metabolism in a manner reminiscent of injury. Of these mediators, the cytokine class of polypeptides are most readily identifiable as eliciting systemic inflammatory reactions (Tracey *et al.* 1988) and of influencing cellular substrate processing in this fashion (Lee *et al.* 1987; Warren *et al.* 1987). The nature of systemic and tissue responses elicited by cytokines has been discussed and several *in vivo* properties of these proteins attest to their participation in the metabolic alterations associated with severe injury (for review, see Klasing, 1988; Moldawer *et al.* 1988; Tracey & Lowry, 1989; Fong *et al.* 1990a). It is known that the exogenous administration of some cytokines, such as tumour necrosis factor (TNF), elicit an increase in energy expenditure

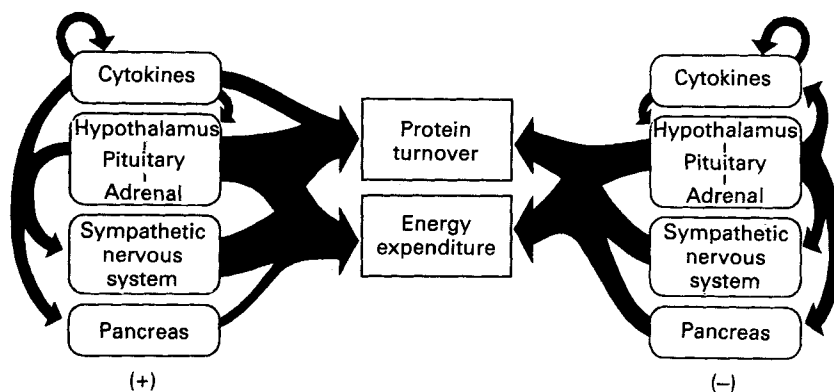


Fig. 1. The potential contribution of various solid organ endocrine stress hormones and cytokines towards regulation of energy and protein metabolism in injured humans. Pathways include those exhibiting an amplification (+) or attenuation (-) of energy and protein metabolism.

as well as enhanced turnover of glucose and free fatty acid pathways (Starnes *et al.* 1988; van der Poll *et al.* 1991). While the appearance of cytokines is also associated with enhanced counter-regulatory hormone activity, this brief macroendocrine stress response, as discussed previously, does not elicit the spectrum of injury-induced substrate turnover (Fong *et al.* 1991).

The extent of cytokine participation in the metabolic response to injury or infection is often difficult to quantify. While circulating forms of these proteins may exert their influence via endocrine means, significant biological responses likely occur at tissue concentrations below those readily detectable by current assays. Additionally, cytokines are produced in response to a diverse array of inciting antigens and do so not only within circulating cells but also at sites of injury and within distant tissues, such as endothelial and Kupffer cells. Some cytokines also exhibit polymorphism, in that several biologically active forms, including cell-associated species, may be expressed (Auron *et al.* 1987; Kriegler *et al.* 1988; Keogh *et al.* 1990).

The most compelling *in vivo* evidence attesting to the influence of cytokines on the metabolic alterations of injured subjects emanates from observations obtained during the *in vivo* blockade of cytokine activity utilizing monoclonal antibodies or receptor antagonists. When animals challenged with bacteria or endotoxin are pretreated with agents directed against cytokines, such as TNF, both the haemodynamic manifestations of this challenge as well as the systemic and regional tissue metabolic responses are attenuated (Tracey *et al.* 1988). Such blockade is also associated with a diminished counter-regulatory hormonal response (Tracey *et al.* 1987a), further evidence for a stimulatory role of cytokines toward induction of the endocrine stress-hormone response. Simultaneous utilization of specific antagonists directed against both cytokines and humoral components will be necessary to further dissect the individual and synergistic contribution of these mediators.

CYTOKINES AND THE CLASSICAL STRESS-HORMONE SYSTEM

Current evidence points to a significant interdependence of the neuro-endocrine axis and of the cytokine mediator systems (Fig. 1). The capacity for augmentation or amplification of the endocrine stress response is demonstrable by the *in vivo* administration of cytokines. For example, the exogenous administration of TNF elicits increased secretion of ACTH and growth hormone in man (van der Poll *et al.* 1991). Less definitive evidence also suggests that cytokines may elicit the secretion of adrenal cortical steroids independent of a pituitary-derived stimulus (Bernardini *et al.* 1990). A sympathetic nervous system response also attends cytokine administration (Tracey *et al.* 1987*b*; van der Poll *et al.* 1991) and the temporal relationship between cytokine administration (Warren *et al.* 1987; van der Poll *et al.* 1991) or induced appearance (Fong *et al.* 1990*b*), suggests a direct influence of cytokines upon sympathetic nervous system activation. The macroendocrine stress hormone system may likewise exert an enhancing influence upon cytokine production. This is evident *in vitro* where noradrenaline has been shown to augment endotoxin-induced TNF production (Spengler *et al.* 1990) and in growth hormone augmented cytokine production by macrophages from hypophysectomized animals (Edwards *et al.* 1991).

These inter-dependent mediator systems also exhibit a countervailing negative feedback system. Such a relationship is most clearly demonstrable in the negative regulatory role exerted by glucocorticoids on TNF and interleukin-1 transcription and post-translational processes. This regulatory capacity of glucocorticoids on cytokine synthesis appears to be transient both *in vitro* (Beutler *et al.* 1986) and *in vivo* as prolonged latency periods between steroid exposure and antigenic challenge can amplify the cytokine response (Barber *et al.* 1990). The cytokines may also serve to attenuate the magnitude of the post-injury metabolic response by direct influences on hypothalamic and pituitary hormone production. This is evidenced by the rapid evolution of a thyroid hormonal profile resembling that commonly observed in critically ill patients (van der Poll *et al.* 1990). Such a response may serve to limit the degree of catabolic processes in critically ill patients.

The inter-dependent and symmetrical natures of the neuro-endocrine and cytokine signalling systems probably promotes, at least initially, a degree of host metabolic and immunological modulation appropriate to the magnitude of the injury. If this challenge is of a modest, reparable magnitude and of limited duration, the initial counter-regulatory hormone and cytokine responses promote the mobilization of energy stores and the maintenance of substrate availability for critical organ function. By contrast, the stress hormonal and cytokine responses to prolonged injury conditions serve to erode host metabolic and immunological reserves. Recent findings also suggest that responsiveness of the microendocrine (cytokine) system may be differentially affected by unstressed malnutrition (Schattner *et al.* 1990) as opposed to conditions of undernutrition in association with stress (Luger *et al.* 1986). Although the mechanisms and functional significance for this differential alteration in cytokine responsiveness remain unclear, it has been suggested that this diminished cytokine responsiveness portends poorly for injured patients. Alternatively, in the absence of repeated or ongoing antigenic challenges, this attenuation of cytokine production during stress may be teleologically appropriate for the preservation of metabolic reserves and for limitation of cytokine-induced tissue injury.

Table 2. *Isotopically determined substrate turnover in severely injured and septic patients the response to total parenteral nutrition*

(Mean values with their standard errors)

	Turnover rates ($\mu\text{mol/kg per min}$)				Net protein catabolism (g/kg per d)	
	Endogenous glucose ($\mu\text{mol/kg per min}$)		Free fatty acids ($\mu\text{mol/kg per min}$)		Mean	SE
	Mean	SE	Mean	SE		
Normal subjects	13.9	0.4‡	5.8	0.4‡	1.44	0.4‡
Patients: Basal						
Trauma	20.8	1.5‡	8.1	1.9‡	2.4	0.2‡
Sepsis	22.2 (est)		13.1	3.0†	2.2	0.1§
Patients: During TPN*						
Trauma	11.0	2.2‡	5.0 (est)‡		1.3	0.5‡
Sepsis	12.0 (est)†		5.6	1.9†	0.6	0.3†

* While receiving 2000–2500 kcal/d (50% of non-protein energy as lipid).

† Shaw & Wolfe (1987).

‡ Shaw & Wolfe (1989).

§ Shaw *et al.* (1987b).

est, estimated; TPN, total parenteral nutrition.

NUTRIENT MODULATION OF THE HORMONAL AND CYTOKINE INJURY RESPONSE

The capacity to influence net loss of lean tissue mass during the height of the injury flow phase appears limited. The mere provision of energy and N excess, with attendant increases in insulin, are insufficient to overcome the systemic immunological dysfunction and net body and lean tissue catabolism associated with injury (Herndon *et al.* 1987; Cerra *et al.* 1988; Fong *et al.* 1990c; Moller-Loswick *et al.* 1991; Pitkänen *et al.* 1991). Isotopically determined alterations in substrate turnover before and during nutritional support of critically ill patients confirm the extent of these persistent catabolic influences (Table 2). Although the mechanisms giving rise to this net anabolic failure remain partially obscure, it is increasingly evident that classical hormonal influences as well as those of cytokines are both contributory to this process. Efforts directed at selective blockade of excessive adrenergic influences in this setting have also failed to fully eliminate the extensive losses of body N in a clinically meaningful manner (Shaw *et al.* 1988).

Recent findings suggest that the route of nutrient delivery may influence the magnitude of the early flow phase catabolic response (Fong *et al.* 1989; Moore *et al.* 1989; Lowry, 1990). Utilizing the acute-phase response as an index of underlying metabolic stress, injured patients receiving nutrients via the intestinal tract exhibit a more favourable maintenance of acute-phase reactants than do cohorts receiving nutrients by vein. The mechanisms underlying the influence of route of nutrient provision on the stress response remain unclear. It is purported that the lack of (appropriate) nutrient provision leads to disruption of the intestinal mucosal barrier function to the extent that bacterial toxins may egress the intestinal lumen. Presumably these toxins, either directly

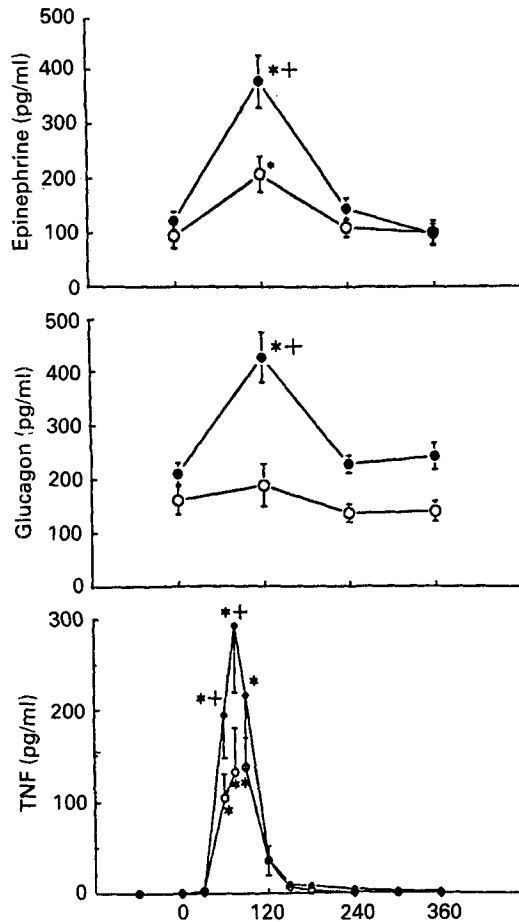


Fig. 2. Hormonal and tumour necrosis factor (TNF) levels in response to endotoxin. Epinephrine, glucagon, and TNF levels in arterial blood before ($t=0$) and after intravenous endotoxin administration. Subjects were studied 12 h after the cessation of 7 d of enteral feedings (○—○) or total parenteral nutrition (●—●). Points are means with their standard errors represented by vertical bars. * $P<0.05$ vs. $t=0$. + $P<0.05$ vs. TPN.

or via activation of immune cells within the intestinal wall, generate sufficient mediator signals to amplify both splanchnic and systemic metabolic processes. Both experimental and clinical findings to support this mechanism have been presented. It has been demonstrated that parenteral nutrition is associated with increased levels of cell-associated TNF within hepatic tissues (Rock *et al.* 1990). Further, when normal humans are fed intravenously for a 1-week period and then exposed to systemic endotoxin, both classical counter-regulatory hormone and cytokine responses exceed those observed in orally fed subjects (Fong *et al.* 1989; Fig. 2). This parenteral feeding-related response is associated with an increased core temperature and enhanced acute-phase protein production.

It has been suggested that alterations in the composition of nutrient formulas may promote beneficial effects with respect to attenuation of hormonal and cytokine

responses in stressed patients (Wilmore, 1991). Although such dietary modifications may have little impact on the initial metabolic responses to injury, their utility may, like that exerted by the route of feeding, be more evident during subsequent stressful situations or during the rehabilitative phase.

STRATEGIES FOR MODULATING THE METABOLIC RESPONSE TO INJURY

The progressive deterioration of immunological and critical organ function attending severe injury or infection remains a vexing challenge (Cerra, 1987). A decline in organ system function coexists with a failure to prevent erosion of host lean tissue and energy stores. Recent advances in our understanding of the potential mechanisms for these events have generated enthusiasm for active intervention against one or more purported mediator systems. While it can reasonably be assumed that both the neuro-humoral as well as cytokine mediator systems contribute significantly toward the metabolic and immunological alterations of complicated injury, the extent of their participation, either singly or in combination, at any given phase of injury remains to be fully determined. As discussed previously, a degree of both positive and negative signal modification may be operative throughout the injury and recovery process. Hence, a perspective of the balance between hormonal and cytokine influences and their potential for beneficial or adverse consequences is mandatory before appropriate interventional efforts are undertaken.

Acute interventions. The majority of clinical efforts directed towards modification of metabolic responses have been pursued during the flow phase of injury. Several such strategies have been investigated, although few have effectively achieved the goal of abrogating hypermetabolism and lean tissue dissolution following severe injury or infection. Unlike those studies invoking blockade of afferent neural signs (Brandt *et al.* 1978; Shaw *et al.* 1987a) in modestly injured subjects, those directed toward blockade of excessive adrenergic activity in more critically injured subjects have demonstrated only modest improvements in substrate turnover and N balance variables (Wolfe *et al.* 1987; Shaw *et al.* 1988). Other acute interventions directed toward anabolic enhancement have likewise proven of only modest benefit during the height of the injury flow phase.

Other efforts have focused on modulating biochemical events which are likely or known to propagate immunological and metabolic dysfunction in the severely injured. Towards this end, interruption of cyclo-oxygenase pathways has received some attention. While such therapy appears to abrogate much of the symptomatology and some clinical manifestations of modest inflammatory challenge (Michie *et al.* 1988a,b), the longer-term consequences of such treatment in terms of immunological function or attenuation of net protein catabolism remain unanswered. It is also likely that strategies directed against alternative components of these pathways, such as blockade of phospholipase A₂ (EC 3.1.1.4) activity, may prove equally effective and less globally immunosuppressive.

Preclinical studies would suggest that interventions directed against the cytokine mediators will benefit some patients during the early phase of severe infectious challenge (Tracey *et al.* 1987a). Prospective clinical trials to address these issues are currently under way. In a manner similar to that achieved with therapy directed against endotoxin (Ziegler *et al.* 1991), anti-cytokine therapies may also prove effective against infection-related mortality and organ system dysfunction. Therapies directed against the more

proximal elements of the cytokine cascade, such as TNF or interleukin-1, are appealing in that these therapies may counteract the early mediators arising from a diverse array of inciting factors, including bacteria, viruses, and severe tissue injury. At present, the clinical scenario most appropriate for application of these antagonists is limited to acute bacterial or endotoxin-induced injury. It will be of significant interest to determine whether these interventions effectively abrogate the more extended metabolic consequences attributable to excessive cytokine activity or, as is more likely, demonstrate only a modest impact on the metabolic alterations associated with infection.

Later interventions. Given the current inability to effectively attenuate the early metabolic disruptions associated with severe injury and the unknown longer-term clinical efficacy of anti-cytokine therapies, it is likely that a proportion of critically ill subjects will continue to manifest both systemic and organ specific resistance to such therapies. Consequently, efforts directed at combined therapies against multiple components of the mediator cascade may be advocated as a means of globally interdicting the injury response. As discussed previously, our understanding of such therapies respective to their influences upon immunological and metabolic function remains limited. Given the likelihood that beneficial influences of cytokines and other mediator systems may be adjuncts to the recovery process, such interventions may, conceivably, invoke untoward adverse consequences. It also remains to be established whether these patients will benefit from repeated administration of response modifying agents directed against cytokines or other mediator systems. While the failure to influence the late sequelae of injury and sepsis by conventional means lends promise to such strategies, it will be necessary to reassess the balance between the stress hormone and micromediator environment evoked by other previous therapies before such interventions can be logically undertaken.

Superimposed on the inability to pharmacologically influence post-injury metabolic responses is the frustration derived from the apparent failure of nutrient intake to influence the post-injury response (Shaw & Wolfe, 1987). Although severely injured patients exhibit a degree of insulin resistance as well as increased lipolysis, such subjects appear to adequately oxidize these substrates and a lack of energy supply does not appear responsible for the continued losses of N and progressive lean tissue wasting (Jahoor *et al.* 1989). Given the degree to which neuro-humoral components are known to influence injury-induced metabolic processes, the complete attenuation of such responses might not be expected (Shaw *et al.* 1988). Unfortunately, other variables which are presumptively sensitive to nutrient intake, such as immune and solid organ system functions, are likewise not beneficially influenced in this setting (Herndon *et al.* 1987; Cerra *et al.* 1988). As the nutrient environment increasingly appears to interface with the endocrine and immunological systems in complex fashion, doubtless alterations in the composition and manner by which critically ill patients are nourished will prove an additional means of response modification.

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