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METABOLIC AND NUTRITIONAL CONSEQUENCES OF THE ACUTE PHASE RESPONSE

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An adequate provision of macro- and micronutrients is necessary for maintenance of an optimal nutritional status during the acute phase response (APR) in order to promote wound healing and prevent malnutrition-related complications. Micronutrient provision has been less well studied than macronutrient provision. This review outlines the metabolic response to injury and the interrelated effects of the APR on macro- and micronutrient status so as to provide a rational basis for specialised nutritional support.

Trauma is the leading cause of death in the first four decades of life and the third leading cause of death for persons of all ages, following cardiovascular disease and cancer.¹ Following trauma or other tissue injury the host initiates a series of complex reactions in an effort to prevent ongoing tissue damage and to facilitate the repair of damaged tissue and to restore tissue function to normal. The immediate set(s) of reactions that are so induced are collectively known as the acute phase response (APR). A coordinated sequence of processes is initiated at the site of trauma, leading to the release of soluble mediators that initiate the metabolic response to trauma.

Resuscitation is the first priority in the management of injury, followed by specific treatment. A major factor that improves outcome in trauma, or injury in general, is the preservation of nutritional status.² Although the majority of trauma victims are healthy and well nourished prior to hospitalisation, the hypermetabolism that is associated with multiple injuries can rapidly lead to severe wasting of lean body mass. Post-injury hypermetabolism leads to malnutrition much more rapidly than simple starvation, and consequently nutritional support is an important part of the overall management of such patients.³ It is thus imperative that the nutrition support practitioner has an understanding of the metabolic response to injury to intervene effectively with specialised nutritional support during a prolonged course of hypermetabolism, immobilisation and healing.

It is known that appropriate nutrition support is positively

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associated with successful recovery.⁴ The maintenance of an optimal nutritional status during the APR to promote wound healing and prevent infections is also well documented.^{5,6} In addition, a wealth of information exists on the effect of the APR on macronutrient status,^{2,6-8} while micronutrient status remains a relatively unexplored field.⁵

The purpose of this article is to review the metabolic response to injury briefly with reference to the various mediators of metabolism. Additionally, the effect of the APR on macro- and, especially, micronutrient status as well as current recommendations on the nutritional management of such patients will be discussed.

METABOLIC RESPONSE TO INJURY

The impact of stress, trauma and sepsis on metabolism is probably best appreciated by its comparison with the starving state (Table I).⁹ In the latter, adaptive homeostatic responses occur, reducing energy expenditure and urinary nitrogen excretion.¹⁰ Metabolism in starvation is primarily aimed at limiting energy expenditure and conserving visceral nitrogen.¹¹ In contrast, the response to injury causes the activation of mediator-effector systems¹⁰ that result in hypermetabolism, hypercatabolism, lipolysis and skeletal muscle proteolysis.¹² Teleologically, this response is thought to decrease the extent and duration of injury and to promote wound healing by mobilising endogenous nutrients into the amino acid and glucose pools.^{2,11}

The accelerated breakdown of skeletal muscle following significant injury was first described by Cuthbertson more than 70 years ago.¹³ Several years later he divided the response to injury into the well-known ebb and flow phases.¹⁴ The ebb phase, occurring immediately after injury, corresponds to the period of hypovolaemia, shock and tissue hypoxia. Characteristics of this phase include a decrease in metabolic rate, cardiac output, oxygen consumption and body temperature. On the other hand, the flow phase (which follows fluid resuscitation and restoration of oxygen transport) is characterised by an increase in cardiac output, oxygen consumption, body temperature, energy expenditure and total body protein catabolism.¹⁴

After injury, catabolism is increased in order to meet the attendant increased energy and protein requirements. Energy expenditure is significantly increased depending on the type of injury.^{10,11} A reprioritisation of protein synthesis occurs¹⁵ which leads to a significant increase in acute phase proteins (fibrinogen, C-reactive protein (CRP), ceruloplasmin, haptoglobin, complement components)^{11,16-18} due to an increase in hepatic synthesis.¹⁹

The metabolic adaptation of the flow phase occurs in two phases. During phase one the increased glycogenolysis and gluconeogenesis contribute to the catabolism of stored sources

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Table I. Metabolic response to starvation and injury*

	Starvation	Injury
Typical setting	Chronic disease	Hospitalised/ICU patient
Energy expenditure	Decreased (↓)	Increased (↑↑)
Stress	Negligible	Severe
Mediator activation	—	↑↑↑
Primary fuel (RQ)	Lipids (0.75)	Mixed (0.85)
Catabolism	Unchanged	↑↑↑
Proteolysis	↑	↑↑↑
Visceral muscle	± N	N/↓
Somatic muscle	↓	↓
Branch-chain oxidation	↑	↑↑↑
Hepatic protein synthesis	↑	↑↑↑
Serum albumin	N/↓	↓↓↓
Ureagenesis	↑	↑↑↑
Urinary nitrogen loss	↑	↑↑↑
Gluconeogenesis	↑	↑↑↑
Insulin secretion	↓	↑ (resistance)
Counterregulatory hormones	Basal	↑↑
Ketone body production	↑↑↑↑	↑
Body weight	↓↓	↓
Body fat deficits	↓↓	↓
Body protein deficits	↓	↓↓

* Adapted from reference 9.
ICU = intensive care unit; RQ = respiratory quotient; N = normal.

of carbohydrate, protein and fat. The counterregulatory hormones (glucagon, catecholamines and glucocorticoids) drive these processes with resultant hyperglycaemia and large nitrogen losses. Insulin resistance occurs even in the presence of large quantities of insulin in the circulation.⁸ The second or anabolic phase occurs as the secretion of the counterregulatory hormones gradually diminishes.¹⁷ During both phases the provision of appropriate energy and protein are essential to ensure wound healing.²⁰

MEDIATORS OF METABOLISM

Metabolism during the APR is influenced by various factors and consists of an interaction between the neuro-endocrine response to trauma, biochemical mediators and a decrease in the intake of nutrients.⁸

Neuro-endocrine response to trauma

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Injury and infection are followed by a series of well-described neuro-hormonal events that include activation of the sympathetic nervous system, stimulation of the hypothalamic-pituitary-adrenal axis and an increase in the secretion of glucagon relative to that of insulin.²¹ The metabolic response to injury is accompanied by elevated serum concentrations of cortisol, catecholamines, glucagon, growth hormone,

aldosterone, antidiuretic hormone,² thyroid stimulating hormone, thyroxin and vasopressin.²² These hormones produce significant increases in metabolic rate and alterations in metabolic priorities. Their levels gradually decrease as the stress phase resolves in parallel with transition to an adaptive (starvation) metabolism, in which fat becomes a primary energy source and fewer demands are made upon the lean body mass.²

The neuro-endocrine response to trauma results in an exaggerated mobilisation of metabolic substrates and a loss of the adaptive decrease in resting energy expenditure (REE) and nitrogen excretion seen in starvation. In contrast to the substrate dependency of uncomplicated starvation, trauma and injury are neuro-endocrine-driven processes.²³ The hormonal response produces a rapid breakdown of body protein and a quick and maximal rate of fat oxidation. Endogenous sources of fuel are the primary energy source.²

It appears that while both catecholamines and glucagon accelerate gluconeogenesis, catecholamines alone stimulate glycogenolysis. Epinephrine and growth hormone on the other hand accelerate lipolysis. These factors lead to the increase in glucose production and the characteristic hyperglycaemia seen in injury.²⁴ Triglycerides are metabolised to glycerol and free fatty acids, which serve as a primary fuel source.^{2,17} Cortisol and glucagon are known to accelerate ureagenesis, resulting in

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increased urinary nitrogen excretion. Water and sodium are retained secondary to the actions of increased concentrations of antidiuretic hormone and aldosterone.²

The blood concentration of these hormones does not, however, appear to be sufficiently high to solely account for the severity of the metabolic upheaval.¹⁶ Additionally, the hypermetabolism and derangements in protein metabolism continue long after plasma levels of catecholamine, glucagon and cortisol have returned to normal.¹⁶ More recently, various other potential mechanisms have been proposed to explain these discrepancies with considerable attention having been focused on cytokines as mediators of metabolism after injury.¹⁷

Biochemical mediators

Cytokines are polypeptides synthesised by cells of the reticulo-endothelial system¹⁷ which are involved in signalling between the cells of the immune system and in modifying metabolism.²⁵ The two, principal, proximal cytokines, interleukin 1 (IL-1) and tumour necrosis factor (TNF- α), both of which stimulate the production of a third, pivotal cytokine, interleukin 6 (IL-6), are released by macrophages after an insult to the host⁶ and are described as pro-inflammatory cytokines as they are key mediators of inflammation.²⁵ Working in a cascade fashion these cytokines not only mediate and modulate an enhanced level of activity in the immune, haematopoietic and cardiorespiratory systems but they also bring about widespread metabolic changes (Table II).^{25,26}

Many of the signs and symptoms experienced during infection and following injury and surgery, such as fever, loss of appetite, weight loss, negative nitrogen and micronutrient balance as well as lethargy, are caused directly and/or indirectly by pro-inflammatory cytokines. Indirect effects of cytokines are mediated by actions upon the pituitary and adrenal glands and endocrine pancreas, resulting in increased secretions of the catabolic hormones adrenalin, noradrenalin,

glucocorticoids and glucagons.²⁷ Recent studies, investigating the metabolic effects of interferon-gamma (IFN- γ), suggest that IFN- γ might also be playing a major role in the metabolic response to infection and injury.²⁸ Cytokines are also known to be responsible for the alterations seen in energy expenditure, gluconeogenesis, lipolysis, vascular permeability and skeletal muscle proteolysis.¹¹ Additionally, the increased hepatic synthesis of acute phase proteins is triggered by the release of cytokines (Fig. 1).¹¹ The production of cytokines is part of the highly effective mechanism for creating a hostile environment for pathogens while promoting healing.²⁹ The essential nature of cytokines in recovery from infection and trauma is indicated by the poor prognosis of malnourished patients, who have a reduced ability for cytokine production.³⁰

This systemic inflammatory response syndrome (SIRS) is clinically identified by an elevation or decrease in white blood cell count, increase in heart rate, raised or subnormal body temperature and changes in respiratory rate or arterial oxygen concentration when breathing room air.³¹ It is generally accepted that in the vast majority of cases the various effects of SIRS lead to an improved outcome from injury, infection or inflammation of limited duration in the previously well-nourished host.

Balancing this pro-inflammatory cascade is the so-called compensatory anti-inflammatory response syndrome (CARS).³² It has been hypothesised, from a growing body of research data, that the relative balance between SIRS and CARS has an impact on survival. IL-6 is partially, while interleukin 4 (IL-4) and interleukin 10 (IL-10) are principally, immunosuppressive and counter-inflammatory. Certain of the eicosanoids, such as the leukotrienes, can enhance cytokine secretion, while others like prostaglandin E₂ reduce cytokine secretion. Fetuin, a negative acute phase protein, has been shown to reduce TNF production by activated macrophages,³³ while spermine, a polyamine found widely in cells, is produced by actively

Table II. The pro-inflammatory cytokines*

Cytokine	Source	Main cell targets	Main actions
Interleukin 1 α Interleukin 1 β	Monocytes, macrophages	Neutrophils, T and B lymphocytes, thymocytes, skeletal muscle, hepatocytes	Immunoregulation, inflammation, fever (endogenous pyrogen), anorexia, sleep, acute-phase protein synthesis, muscle proteolysis, \uparrow gluconeogenesis, lymphocyte activation, IL-6 and CSF (colony-stimulating factors) production
Interleukin 6	Monocytes, fibroblasts, T cells	T and B lymphocytes, thymocytes, hepatocytes	Acute-phase protein synthesis (synergises with IL-2 in the production of acute phase proteins by hepatocytes), synergises with IL-3 in haematopoietic cell growth, immune cell differentiation, induces CTL (cytotoxic T lymphocyte) differentiation
Tumour necrosis factor α	Monocytes, macrophages	Fibroblasts, endothelium, skeletal muscle, hepatocytes	As for IL-1, induces IL-1, induces IFN- γ secretion

*Adapted from reference 26.

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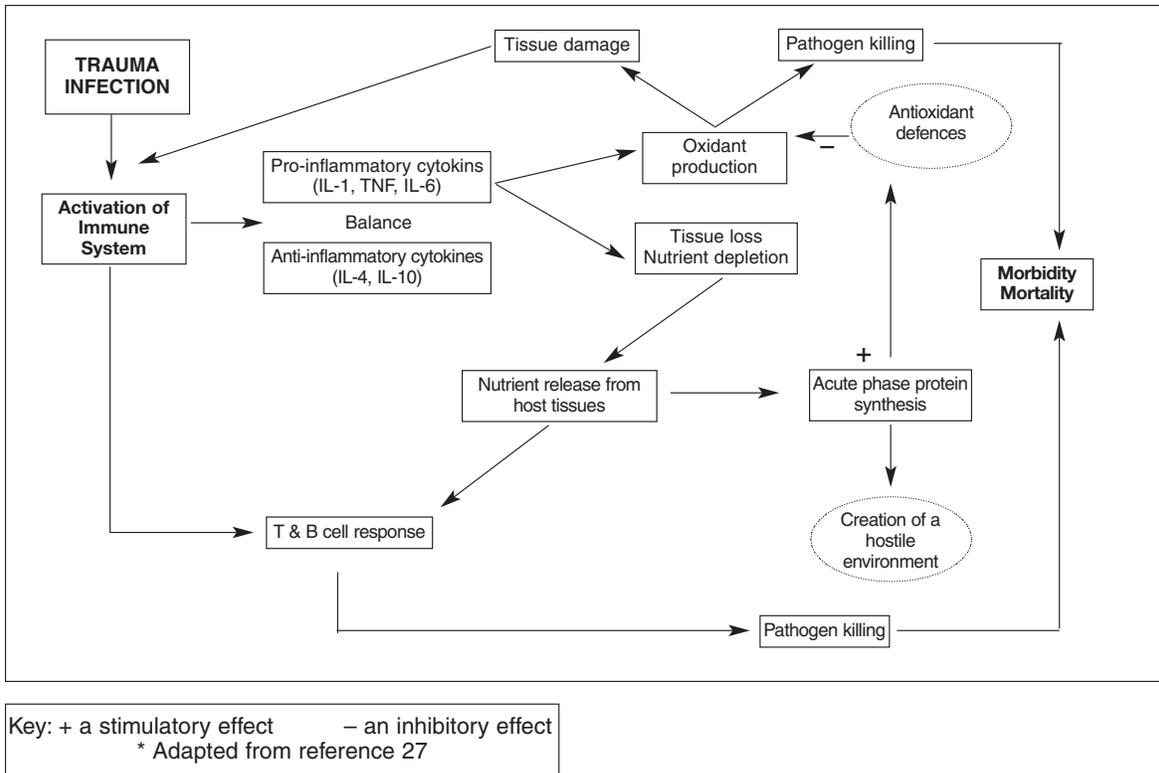


Fig. 1. Key features of the inflammatory response.*

regenerating cells and released by injured or dying cells. Fetuin and spermine are thought to interact to suppress the immune response,³⁴ providing an additional mechanism for the resolution of SIRS.

Under most circumstances these two systems of inflammation and counter-inflammation are carefully balanced leading to inflammation, repair and recovery. However, under certain conditions, which are increasingly realised to be under genetic control, SIRS can be potentially harmful. It has been demonstrated that IL-1, TNF and IL-6 levels are directly correlated with the severity of illness as well as subsequent morbidity and mortality.³⁵⁻³⁷ The pro-inflammatory cytokines may also play a detrimental role in inflammatory disease and atheromatous plaque development. The excessive production of pro-inflammatory cytokines due to repetitive episodes of less severe SIRS or overwhelming illness are thought to play an important aetiological role in the development of multiple systems organ failure.³⁸ A number of clinical studies indicate that not only is a capacity for high production of pro-inflammatory cytokines deleterious to health and survival, but enhanced production of anti-inflammatory cytokines is also disadvantageous. An excessive CARS, represented by higher

levels of IL-10 in relation to TNF, can lead to heightened immunodepression and poorer outcome.³⁹ It would thus appear that the ratio of pro- to anti-inflammatory cytokines might be a more predictive determinant of outcome than the level of synthesis of either type of cytokine alone. High IL-6 to IL-10, and IL-10 to TNF- α , ratios are associated with increased mortality.^{39,40} Therefore it would appear that it is not only the pro-inflammatory and the anti-inflammatory components of the cytokine mediators that need to be well controlled, but the relationship between the two must also be appropriately proportionate.

Dietary intake

Various factors related to the APR lead to a diminished intake of nutrients. These include direct gastrointestinal injury, inability to ingest food because of various treatment modalities (e.g. endotracheal intubation and the anorectic effect of medication) as well as the anorectic effect of various cytokines (especially TNF and IL-1,⁴¹⁻⁴³ IL-6,⁴⁴ interferon,⁴⁵ and IL-8⁴⁶). Anorexia during disease and injury can be beneficial or deleterious depending on its timing and duration. Temporary anorexia during acute disease may be beneficial since a

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restriction in the intake of macro- and micronutrients can inhibit bacterial growth. On the other hand, chronic anorexia compromises host defence, delays recovery,⁴⁷ and is deleterious, leading to cachexia and, ultimately, death. Anorexia induced by cytokines is proposed to involve modulation of hypothalamic feeding associated sites, prostaglandin-dependent mechanisms, modifications of neurotransmitter systems, as well as gastrointestinal, metabolic, and endocrine factors.⁴⁸ Interleukins, in particular interleukin IL-1 β and TNF- α , reduce food intake following peripheral and central administration, suggesting that they contribute to the anorexia during various infectious, neoplastic and autoimmune diseases, as well as after injury.⁴⁹ Because cytokines are mainly produced in the periphery during most of these diseases, IL-1 β and TNF- α may inhibit feeding indirectly through neural and humoral pathways activated by their peripheral actions. TNF- α induces leptin, the body fat regulatory hormone, but, as of yet, no direct role for leptin in the significant weight loss that occurs during infection/injury has been documented.²⁷ Finally, circulating IL-1 β and TNF- α may act directly on the brain or cytokine synthesis in the brain may contribute to the anorectic effect of systemic immune stimulation. Central mediators of the anorectic effects of cytokines appear to be neurochemicals involved in the normal control of feeding, such as serotonin, histamine, α -melanocyte stimulating hormone, corticotropin releasing factor and neuropeptide Y.⁴⁹

The relative neglect by professionals with regard to attending to the nutritional needs of the patient as part of their treatment is cause for concern, especially when one considers the deleterious consequences of the anorexia-cachexia syndrome. Therefore, understanding the specific mechanisms and interactions responsible for disease- or injury-induced anorexia is essential in the development of effective nutrition interventions for the control thereof and for impacting favourably on morbidity and mortality. In this regard, it should also be borne in mind that the adverse effect(s) of diminished nutrient intake is (are) further accentuated by the inability to adapt to a more stable 'starving state' metabolism, which makes the administration of early and effective nutrition support mandatory.

EFFECT OF THE APR ON MACRONUTRIENT STATUS

Energy metabolism

In healthy individuals total energy expenditure (TEE) can be divided into three components: basal metabolic rate (BMR), thermogenesis, and physical work. Lean body mass is the major determinant of BMR, which maintains basic functions and represents 60 - 70% of TEE in sedentary individuals.⁵⁰ Thermogenesis represents \pm 10% and physical activity 20 - 30% of TEE. In the presence of injury/illness two additional components influence the metabolic rate — the first component

is related to the injury/illness itself and the second to the effects of treatment.⁵⁰

Following injury and trauma, increases in REE, which is defined as the summation of basal energy expenditure and the energy required to maintain normal body functions, have been widely documented.⁵¹ Hypermetabolism is a typical feature in severely injured patients and is characterised by a moderate to marked increase in REE, depending on the nature and severity of injury, together with an associated increase in O₂ consumption, cardiac output and CO₂ production.⁵² For instance, REE is usually normal or slightly increased after elective surgery.⁵³ However, after major surgical procedures, REE may be increased up to 120 - 140% of reference values⁵⁴ while in patients with severe trauma requiring intensive care management REE is usually in the 120 - 150% range.⁵⁵ Infection, complicating surgery or trauma seems to produce an additional increase in energy expenditure (EE).⁵⁰ In critically ill patients (median injury severity score (ISS) = 35) REE can rise 55% above predicted (using total body potassium (TBK)) while TEE equals 1.32 x REE.⁵⁶ The finding that REE, as measured by an indirect calorimeter, does not translate into TEE suggests that the mechanically ventilated patient has a component of metabolic expenditure separate from that measured by the indirect calorimeter due to the considerable manipulations that are part of critical care management.

The severity, length and stage of illness influence the level of metabolic rate. In severe uncomplicated trauma, the highest REE is usually reached after 3 - 5 days, declining slowly thereafter, whereas in the presence of surgical or medical complications the REE can remain elevated for prolonged periods (weeks, even months).⁵⁰ In this regard, Monk *et al.*⁵⁶ documented a significant degree of hypermetabolism (35% above predicted REE), which was still evident on day 24 post-injury, suggesting that hypermetabolism may last longer than previously thought. The most extensive hypermetabolism is found in patients with major burns (> 40% burned skin area) where REE may reach 160 - 180%. More recent data, however, indicate that lower values (140 - 160%) are observed with modern surgical and critical care management.⁵⁷

The increase in REE may be due to the following reasons, singly or in combination: (i) increased O₂ utilisation by injured tissues; (ii) increased energy expenditure by other organs (e.g. the heart); (iii) increased substrate recycling (or 'futile cycling' in the traumatised patient) which involves the breakdown and synthesis of glucose and triglycerides, but without a net production of free fatty acids or glucose. Since ATP (adenosine triphosphate) is hydrolysed in these cycles, such recycling represents a net energy drain.^{16,51}

Several other endogenous mechanisms contribute to the hypermetabolism seen in critically ill patients. Hormones (e.g. counterregulatory hormones) and cytokines contribute significantly to hypermetabolism by influencing metabolic rate

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and substrate metabolism.^{58,59} The activation of certain metabolic pathways (e.g. gluconeogenesis, Cori cycle) promotes hypermetabolism by consuming large amounts of energy. Other factors that increase EE in the stressed patient and cause an elevation in metabolic rate include pain, agitation, abnormal posturing, increased muscular tone and seizures. Many drugs and supportive treatments are also known to influence REE.⁵⁰ Fever, a common finding in traumatised patients, is also an energy consuming process, inducing a 10 - 15% increase in EE for each degree Celsius elevation of temperature. Cytokine release and the release of endogenous pyrogens⁷ also induce a resetting of the hypothalamic thermoregulatory set-point to a higher value, thus initiating fever.

Trauma profoundly alters energy metabolism with the characteristic elevation of REE. Several factors influence EE in the critically ill, making the prediction of REE extremely difficult and unreliable. Current recommendations indicate that indirect calorimetry should preferably be used, where and when possible, for the direct measurement of REE in the critically ill patient for optimal energy provision.⁵⁰

Protein metabolism

The metabolic response to injury/trauma involves an increased loss of body proteins. A cascade of events is initiated that leads to accelerated protein degradation, increased amino acid catabolism and nitrogen loss. In the liver, the rate of synthesis of selected proteins (i.e. albumin, transferrin, prealbumin, retinol binding protein (RBP) and fibronectin) is decreased, whereas acute phase protein synthesis is accelerated.⁶⁰

Changes in protein and amino acid metabolism occur mainly in certain identified sites. These include skeletal muscle, the liver and rapidly dividing cells (e.g. traumatised tissue and the immune system). Net protein catabolism is accelerated post-injury with the result that severely ill patients may lose up to 20% of their body protein, mainly from skeletal muscle.⁶¹ Prolonged immobility of patients may additionally cause atrophy of skeletal muscle and also contribute to further nitrogen loss.⁶⁰ The result is a negative nitrogen balance even in the face of increased total protein synthesis.⁷ Skeletal muscle

contains 80% of the body's free amino acid pool, of which 60% is glutamine.⁵¹ At this level, various changes in amino acid flux take place and are characterised by the peripheral, skeletal mobilisation of amino acids from muscle, especially alanine and glutamine.⁸ This is mirrored by an increased hepatic uptake of these amino acids which serve as substrates for protein synthesis (acute phase proteins) and fuel gluconeogenesis.⁸ The increased release of amino acids also provides for alternative energy substrates for the gut (e.g. L-glutamine).⁵¹ A key role for L-glutamine, the intracellular concentration of which falls in skeletal muscle by approximately 50% after trauma,⁶² is its utilisation by the gut and other rapidly proliferating tissues (e.g. lymphocytes) as a fuel.^{51,63}

Despite the apparent usefulness of protein catabolism in these circumstances, severe depletion of lean body mass increases morbidity and mortality in the acute phase and delays the recovery from illness.^{60,64} A recent study⁵⁶ in critically injured patients demonstrated a 16% loss of total body protein of which 67% came from skeletal muscle over a 21-day study period. This degree of loss profoundly affects muscle function and, hence, weaning from the ventilator and convalescence. In this study, protein losses were considerable despite enriched enteral feeds (containing glutamine at 14.2 g/l and arginine at 1.8 g/l) indicating that protein loss is not influenced entirely by the amount of protein administered.⁵⁶

One of the major components of the APR to injury or infection is the change in the concentration of a large number of plasma proteins referred to as acute phase proteins (APP). The APP are a group of approximately 30 plasma proteins synthesised in increased amounts principally by hepatocytes, following injury or infection.⁶⁵ The post-injury period in the liver is thus characterised by a selective increase in the synthesis of APP.⁶⁰ Kushner⁷ has defined APP as those proteins which rise in plasma concentration by 25% or more following inflammation, and has divided them into three groups⁶⁶ on the basis of the magnitude of the increase. The most marked increase occurs in the 'true' acute phase proteins, CRP and serum amyloid A protein (up to 1 000 x increase).^{8,22,65} Some authors have classified APP as either positive or negative (Table III).^{22,67} Those proteins with concentrations that are

Table III. The major human acute phase proteins^{7,22}

	Positive APP		Negative APP
Low rise: ± 50% increase	Moderate rise: 2 - 4x increase	Marked rise: up to 1 000x increase	Decreased plasma concentrations
Caeruloplasmin	Orosomuroid	C-reactive protein	Albumin
Complement C3	α ₁ -acid glycoprotein	Serum amyloid A	Pre-albumin
Complement C4	α ₁ -antitrypsin		Transferrin
	α ₁ -antichymotrypsin		RBP
	Haptoglobin		Fibronectin
	Fibrinogen		

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increased are referred to as positive APP (e.g. fibrinogen, CRP, serum amyloid A, ceruloplasmin, haptoglobin, complement components), and those with levels that decline are termed negative APP (e.g. albumin, transferrin, pre-albumin, RBP and fibronectin).⁶⁷

The observation that local injury at distant sites leads to the APP response implies the existence of circulating messengers, which induce hepatic stimulation. In this induction of APP synthesis, cytokines play a central role.⁶⁷ The rises detected in APP concentrations are thus the result of increased hepatic synthesis as mediated by various cytokines.^{8,65,67} IL-6 is considered a long-distance alarm signal that alerts the hepatocytes to the presence of tissue damage.⁶⁷ The roles of IL-1 and TNF- α are considered to be primarily of a local nature whereas that of IL-6 is considered both local and systemic.⁶⁷

On the other hand, the concentrations of the 'negative' APPs decrease following trauma^{8,22} and these concentrations remain low for the duration of the inflammatory response. The reduced plasma concentrations of negative APP during the APR could result from catabolism, decreased synthesis (preference being given to the synthesis of 'positive' APP), increased transcapillary escape as a result of the increased vascular permeability induced by the release of cytokines,^{8,68} or an altered distribution between the extra- and intravascular compartments.^{8,18,67}

The known biological functions of APP include participation in host adaptation or defence, inhibition of serine proteinases, and transport of proteins with anti-oxidant activity.⁶⁷

Changes in immune function are also an important clinical consequence of protein catabolism. T lymphocyte function is primarily decreased, whereas changes in B cell function are more variable. Complement activity and granulocyte function are also affected.⁶⁰ These changes in immune function are thought to contribute significantly to the immunocompetence of the patient.

The visceral proteins (e.g. albumin, transferrin, pre-albumin, RBP) have traditionally been used for assessment of nutritional status, and have been considered to reflect visceral protein stores.⁶⁹ In the short term, however, they may also reflect the severity of the metabolic response to surgical stress and the prognosis in critically ill patients.⁷⁰ In many clinical situations, it may be difficult to determine whether changes in a patient's serum protein levels reflect nutritional status or are a consequence of the metabolic response to injury.⁷¹ Thus, the visceral proteins, especially albumin, may not be as useful as previously thought as an index of nutritional status, and should be interpreted with caution in the acutely ill.⁸ As a result of the metabolic alterations, alternative indices have been developed for the assessment of nutritional status, which take into account the changes in 'nutritional' and 'inflammatory' proteins. An example is the Prognostic Inflammatory and Nutritional Index (PINI), which was described by Ingenbleck

and Carpenter⁷² as a means of distinguishing between nutritional deprivation and metabolic stress is such an example. The index combines multiple serum proteins such as albumin, thyroid binding pre-albumin (TBPA), CRP and alpha-1 acid glycoprotein (AGP), and is considered more valuable for assessing nutritional status than the determination of single visceral proteins.⁷¹

The described alterations in protein metabolism clearly have practical implications for the nutrition support practitioner. The provision of adequate nitrogen (N) in the correct composition has been actively investigated. Optimal nutrition support has been shown to decrease morbidity in the critically ill patient by maintaining immunocompetence,⁷³ improving wound healing and preventing infections.⁵⁶ However, nutrition seems to be relatively ineffective in the prevention of the massive loss of lean body mass that follows severe trauma^{60,61} and several reports indicate that a positive nitrogen balance cannot be achieved in severely traumatised patients.⁷⁴ In this regard, a number of studies have shown that even during aggressive nutrition support with positive energy balance and large nitrogen supply, nitrogen balance remains negative during periods of high stress.⁵⁰ During such periods, the use of amino acids for glucose and energy production is increased when compared with normal subjects and the contribution of protein to energy production is increased. Consequently, there is a reduction in net protein synthesis.⁷⁵ Thus, tissue catabolism remains elevated even in patients receiving adequate energy and nutrient supply, indicating a state of nutritional resistance.⁵⁰

A number of therapeutic approaches have been developed in an attempt to improve the protein anabolic efficacy of conventional nutrition. These include hormones (insulin, growth hormone, insulin-like growth factor 1), medications (pentoxifylline, amrinone, β_2 -agonists) and metabolites (arginine, omega-3-fatty acids, glutamine, alpha-ketoglutarate, ornithine alpha-ketoglutarate, and carnitine).⁶⁰ These approaches have been shown to affect protein metabolism positively in the clinical setting or in experimental conditions,⁶⁰ but further research is necessary to clarify the role of each in the acute setting.

Carbohydrate metabolism

Carbohydrate metabolism during the APR is marked by various degrees of hyperglycaemia,⁷⁶ decreased glucose tolerance and insulin resistance.^{8,77} These characteristics are the result of increased glycogenolysis^{8,16} and non-suppressible gluconeogenesis from substrates mobilised peripherally.^{8,16,78}

New glucose enters the plasma either from external sources (i.e. absorption from the gastro-intestinal tract or intravenous infusion) or via endogenous production from glycogen (glycogenolysis) or other precursors such as amino acids (gluconeogenesis).^{51,79} The post-trauma period is characterised

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by an increase in hepatic glycogen breakdown⁵¹ and an associated reduction in the peripheral utilisation of glucose.^{76,80} The net result is an increase in plasma glucose concentration and an increase in insulin release. Under normal conditions the glucose production rate is inversely linked to plasma glucose concentration. During the post-injury period, however, the liver produces glucose at an increased rate under the influence of hormones and cytokines such as glucagon and IL-1 respectively.⁵¹ Experiments involving infusions of glucagon, adrenaline and cortisol in man have shown that these hormones act synergistically to promote hepatic glucose output.⁸¹ Glucose production is therefore increased despite an increased blood glucose concentration.

In healthy individuals gluconeogenesis is inhibited by an increase in blood glucose levels. In the trauma patient, however, hepatic glucose production is increased despite the hyperglycaemia characteristically seen in this group of patients. Hepatic gluconeogenesis normally occurs at a rate of approximately 2.0 - 2.5 mg/kg/min, but it increases to at least 3.5 - 5.0 mg/kg/min in the stressed state. This contributes to the requirements of glucose-dependent tissues including the brain and, to some degree, the kidney, liver and skeletal muscle.³ The suppression of gluconeogenesis by glucose infusion is much less effective in trauma patients than in healthy volunteers,^{82,83} probably due to the increased availability of gluconeogenic substrates.^{76,84} In severely stressed patients, muscle glycogenolysis and the metabolism of hypoxic tissue produce lactate, glycerol is released from adipose tissue and plasma alanine levels are increased as a result of enhanced proteolysis.^{16,79} It has been shown that lactate is quantitatively the most important gluconeogenic substrate in burn patients⁷⁶ followed by alanine, glycerol and pyruvate, in that order of importance.⁷⁹ Trauma patients show a 40% increase in alanine appearance rate and a 100% increase in glycerol appearance rate and the availability of lactate.⁸⁵

Thus, besides the breakdown of glycogen in the liver several other pathways exist for the production of glucose. These pathways include: (i) conversion of lactate (Cori cycle); (ii) production from amino acids (e.g. L-alanine and L-glutamine); and (iii) synthesis from pyruvate.⁵¹ The plasma glucose level, however, provides little indication of glucose turnover. It is generally accepted that glucose turnover is increased during the flow phase following trauma and gluconeogenesis is enhanced despite freely available plasma glucose.¹⁶

The post-injury period is characterised by resistance to insulin as indicated by the elevated concentrations of both glucose and insulin, with a more marked rise in insulin concentrations.⁵¹ Plasma insulin levels rise to reach a peak several days after injury of up to three times basal levels.¹⁶ This coincides with the period of maximal catabolism.¹⁶ The high levels of insulin fail to suppress glucose production, and there is a reduction in glycogen storage, lipolysis and fat

oxidation.^{16,86} Some investigators have reported a significant correlation between plasma insulin concentration and nitrogen loss in trauma patients, thereby suggesting that protein turnover is resistant to the normal anabolic effect of insulin.⁸⁷ Others have demonstrated that insulin acts to conserve protein by restraining the release of amino acids from peripheral tissues.⁸⁸ Experimental studies have implicated glucocorticoids as a cause of insulin resistance, although the mechanism of this response is yet to be defined.⁸⁹

Contradictory information exists on the effect of injury/trauma on glucose oxidation. Some investigators report that glucose oxidation is increased during the post-injury period,^{16,90,91} others conclude that trauma patients oxidise glucose to an extent similar to that of normal volunteers⁹² and yet others conclude that trauma results in an impaired capacity to oxidise glucose.^{93,94} A considerable amount of data derived from isotopically labelled substrate studies suggest that glucose is oxidised less efficiently in patients who have been injured.^{51,85,95}

The cells involved in inflammation and wound repair rely on glucose as a primary fuel that they predominantly metabolise anaerobically. The increased glucose turnover provides essential fuel for inflammatory and reparative tissue, which optimises host defences and ensures wound repair.¹⁶

Lipid metabolism

The findings in lipid metabolism following trauma involve several complex changes in the mobilisation and oxidation of fat. Studies of lipid metabolism have not always yielded a consistent picture with variable changes in plasma levels of triglycerides, free fatty acids (FFA), ketone bodies and very low density lipoproteins (VLDL) being reported.⁷

Lipids represent a significant portion of the substrate oxidised for energy in severely injured and septic patients.³ Lipolysis of triglycerides (sometimes referred to as triacylglycerols) is enhanced immediately after injury.^{3,79,85} This process leads to the production of FFA and glycerol, thereby increasing their turnover rate after injury/trauma.⁵¹ The glycerol can be used by the liver for gluconeogenesis and the fatty acids can also be used as a fuel source (although mammals cannot synthesise glucose from fatty acids).⁵¹ The increase in the rate of lipolysis is brought about by the stimulation of the sympathetic innervation of adipose tissue and by raised plasma adrenaline, glucagon and cortisol levels.⁷⁹ Growth hormone may also be involved in this response.⁹⁶ The accelerated lipolysis occurs despite the prevailing hyperglycaemia and raised plasma insulin.⁸²

In trauma patients the rate of lipolysis (as reflected by glycerol flux) is greater than the FFA appearance into the plasma.⁸⁵ This can in part be explained by the lactic acidosis of systemic hypoxia which encourages re-esterification of triglycerides,^{16,51} with a resultant rise in plasma triglyceride

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levels.⁹⁷ The high rate of fat oxidation, however, suggests that some fat is also oxidised directly in the tissue in which lipolysis of triglycerides occurs.⁸⁵ The reduced perfusion of adipose tissue following trauma, causing an inadequate supply of albumin carriers for released FFA, also contributes to this response.⁹⁸ Since glycerol cannot be phosphorylated peripherally it still appears in plasma as a reflection of lipolysis while the FFA never appear in the plasma.^{85,99}

Cellular uptake of medium and long-chain fatty acids is increased in infected and traumatised patients, suggesting an increased turnover rate relative to plasma concentration.⁸ The levels of the various fatty acids in the plasma also change somewhat with oleic acid levels increasing and linoleic and arachidonic acid levels decreasing.³ Normally, increased tissue lipoprotein lipase (LPL) activity favours the utilisation of triglycerides as oxidative substrates by cardiac and skeletal muscle.¹⁰⁰ However, during stress, lipid uptake into non-adipose tissue is impaired by TNF- α , IL-1 β , and interleukin 2 (IL-2) which inhibit the activity of LPL.¹⁰⁰ Clinical studies indicate that the mechanisms resulting in increased availability of fat substrate appear to dominate because fat oxidation is sustained or accelerated in seriously ill patients.⁸⁶ The increase in fatty acid oxidation in sepsis and trauma is not 'substrate led' as the plasma levels of FFA are often quite low.¹⁶ This suggests that there are changes in the intracellular metabolism of fat in these patients.⁷⁹ The preference for fat as an energy substrate is more pronounced in septic than in trauma patients.¹⁰¹ Monk *et al.*⁵⁶ found that when energy intake fell short of energy requirements, fat was utilised; if energy intake was sufficient, total body fat stores were preserved.

Ketone bodies can serve as alternative energy substrates for many tissues, as they reduce whole body glucose demand and therefore gluconeogenesis from protein. However, in severe sepsis and, to a lesser extent, trauma there is a blunting of the adaptive ketoaemic response and its subsequent nitrogen conservation.^{102,103} Although hepatic production of ketones may be increased, plasma ketone levels are low.¹⁰⁴ It is likely that the increased insulin levels seen in stressed surgical patients are responsible for the impaired production of ketone bodies,¹⁰⁵ although reduced activity of hepatic acylcarnitine transferase has also been implicated.¹⁰⁶

EFFECT OF THE APR ON MICRONUTRIENT STATUS

The APR to injury or infection is associated with alterations in the metabolism of a number of vitamins and trace elements. The exact consequences of the APR on micronutrient status and consequent implications in terms of micronutrient requirements are still largely unknown.

The increased metabolic rate and catabolism associated with the APR are thought to increase the requirements of such micronutrients as vitamins A, E, B₆, C, D and folate.¹⁰⁷⁻¹⁰⁹ It is

also known that a redistribution in plasma trace elements occurs with a decrease in the concentrations of iron (Fe), zinc (Zn) and selenium (Se) and a concomitant rise in copper (Cu) levels.^{67,41,110} It is generally accepted that increased needs due to increased losses are often compounded by decreased intake, especially in surgical patients. Thus, micronutrient deficiency states are a potential clinical problem in seriously ill patients.⁴

Most of the changes that occur in micronutrient status during the early stages of the APR are perceived as host beneficial.^{8,111} If, however, these changes persist for a prolonged period, vitamin and trace element stores may become depleted with important clinical consequences. It is well documented that depleted patients are at high risk for nosocomial infections due to immunosuppression,¹¹² a decrease or delay in wound healing and tissue repair¹¹³ and a loss of muscle strength and diminished activity.¹¹⁴ Maintaining adequate micronutrient stores in the critically ill patient is thus of obvious importance, although this field remains relatively unexplored and recommendations are inconclusive.

CHANGES IN PLASMA CONCENTRATIONS OF TRACE ELEMENTS DURING THE APR

Trace elements are essential for maintaining homeostasis and are an indispensable component of dietary intake. Though it has long been recognised that trace elements represent essential dietary constituents, little is known about their role in critical illness and the body's response to injury. Critical illness induces increased nutritional requirements associated with the attendant hypermetabolic state. Although trace element metabolism is clearly affected by illness, the precise requirements for trace elements in these patients are not known.¹¹⁵

The assessment of trace element status during the APR is particularly difficult, since plasma concentration of these elements may bear little relationship to tissue status.¹¹¹ Traditional biochemical methods for assessing requirements (i.e. measurement of serum or plasma concentration of the element) may provide useful information regarding the development of an under- or over-provision state for elements such as K, Mg and P.¹¹¹ These methods, however, may not reflect the whole-body status of certain trace elements, especially during serious illness.

Highly coordinated changes take place in the plasma concentration of Fe, Zn, Cu and Se after trauma or during illness. These changes appear to be directly under the control of cytokine mediators and probably have little to do with the nutritional status of these elements initially.^{8,111} In spite of much encouraging data suggesting that additional supplementation of trace element intake is beneficial in critical illness, it is necessary to understand their metabolism and various mechanisms of action in the context of the APR, in order to provide an optimal intake that is both adequate and safe.

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MECHANISMS AND BENEFITS OF CHANGES IN TRACE ELEMENT CONCENTRATIONS**Iron**

Serum Fe concentrations have been documented to decrease during infections,^{116,117} after an endotoxin injection¹¹⁸ as well as after cytokine administration.¹¹⁷⁻¹¹⁹ The plasma concentration of Fe falls rapidly after injury, a significant fall being evident within 2 - 4 hours after a skin incision. The concentration continues to fall until 12 - 24 hours after the beginning of surgery. Thereafter, plasma Fe concentration tends to remain low for several days up to 1 - 2 weeks.¹²⁰ Van Iperen *et al.*¹²¹ reported that serum Fe concentrations decreased to 23% and 46% of preoperative levels after major and minor surgery respectively and remained low for up to 28 days after major surgery. Serum transferrin concentrations and transferrin saturation decreased after both types of surgery while ferritin concentrations increased. Serum transferrin receptor concentrations increased only 4 weeks after major surgery.

The fall in plasma Fe results from the transfer of Fe from the Fe-transferrin complex in the plasma to other proteins. Initially Fe is transferred to lactoferrin, released from leucocytes at the sites of inflammation. Fe is then taken up and bound to ferritin in the liver and spleen.^{7,111} Depletion of Fe from serum is thus associated with an increased Fe and ferritin content of the liver. Cytokines, generated by activated T cells and macrophages, orchestrate the removal of iron from the plasma.¹²² The cytokines IL-1, IL-6 and TNF are the major mediators altering Fe dynamics.^{123,124} Even minor tissue damage can initiate an APR, including the release of cytokines, and is sufficient to produce changes in iron metabolism. The main cause of anaemia at this time is increased clearance of Fe into non-haemopoietic tissues.¹²⁵

The movement of Fe into a storage form reduces its availability within the plasma, thereby withholding Fe from bacteria¹²⁶⁻¹²⁸ and reducing the conversion of superoxide radicals to free hydroxyl radicals, thus reducing oxidative damage to membranes or DNA.¹²⁰ The hypoferraemic response that develops during the APR, in relation to trauma or infection, is thus thought to be a protective response^{126,127,129-132} that aids the host by decreasing the availability of iron for use by invading micro-organisms.

Should the abovementioned changes in Fe dynamics persist, Fe transfer to bone marrow is reduced, leading to the anaemia of chronic disease,^{122,133} and in the long term, potential Fe depletion. The degree of 'anaemia of chronic disease' is directly related to the extent of injury.¹²¹

Zinc

An initial increase in serum Zn concentrations and in the zinc/albumin ratio is seen after trauma or surgery, followed by a decrease in both parameters.¹²⁰ This decrease in serum levels

of Zn that occurs in response to physiological stress has been well documented¹³⁴⁻¹³⁹ and may be the result of increased losses, dilution and tissue redistribution of zinc in the presence of the APR.¹⁴⁰

The initial increase in Zn concentrations may be explained by the release of Zn from intracellular stores, in response to tissue damage.¹²⁰ The subsequent decrease in serum Zn is probably partly related to the fall in serum albumin concentrations seen in all seriously ill patients as a result of increased transcapillary escape to the extravascular compartment.¹³⁸ As most plasma Zn circulates bound to albumin, a significant fall in plasma albumin leads to a fall in Zn concentration. During the APR the drop in plasma Zn is usually greater than that in albumin, indicating the active transfer of Zn from its albumin binding site to some other body compartment. The removal of Zn from its main transport protein is thought to be mediated by IL-1.^{41,118}

The proposed mechanism to partly explain this phenomenology may be based on the induction of the low-molecular-weight protein metallothionein.¹⁴¹ The synthesis of metallothionein is induced in the liver and other tissues by cytokines such as IL-1,¹⁴² corticosteroids and heavy metals.^{143,144} It has been demonstrated that IL-1 alone has no effect on the metallothionein response and that the effect of IL-1 is in fact mediated through IL-6.¹⁴³ Metallothionein can extract Zn from albumin and other transport proteins, resulting in increased hepatic Zn concentrations. In this way, the liver extracts Zn, which can then be used for the synthesis of other proteins.¹²⁰

The decrease in serum Zn may also be related to a redistribution of Zn to the site of tissue injury as studies have shown that Zn localises in actively healing wounds.¹⁴⁵ Zn can also decrease in serum as a nonspecific reaction to stress. Surgical trauma increases corticosteroid secretion, which decreases the serum Zn concentration.¹⁴⁶ Hypermetabolic trauma patients may experience excessive gastrointestinal Zn losses.¹⁴⁷ The urinary excretion may also contribute to the low plasma concentration in these patients.¹⁴⁸ Additionally, Berger *et al.*¹⁴⁹ demonstrated high cutaneous Zn losses in thermal injury patients.

Several reasons have been proposed why lowering of serum Zn levels with liver accumulation should benefit the host. These include repair of damaged tissue, protection of the liver from endotoxins, co-factor function in acute phase protein synthesis and increased bacteriocidal capability after phagocytosis.⁸ Zn is also an essential part of the Zn-finger components of the DNA-binding transcription factors, which are important in controlling the selectivity of protein synthesis.¹¹¹ Alterations in Zn levels are also thought to improve host defence mechanisms by prevention of microbial proliferation.¹⁵⁰

Copper

In contrast to the changes seen in Fe and Zn, serum Cu

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concentration rises during the APR as a result of the increased synthesis of its carrier protein, ceruloplasmin as part of the APR.^{7,116,135} Ceruloplasmin synthesis is induced by IL-1 and IL-6.^{151,152} A proposed benefit of the increased ceruloplasmin concentration is that it may play a role in Fe transport as a result of its ferro-oxidase activity.¹¹¹

In contrast, Boosalis *et al.*¹⁹ observed decreased concentrations of Cu and ceruloplasmin in the serum of patients with greater than 40% total body surface area burn, which lasted almost for the full duration of hospitalisation. It was later confirmed that this decline in Cu and ceruloplasmin could be attributed to an antagonistic relationship between copper and silver, a result of the cutaneous absorption of the topical antimicrobial agent, silver sulfadiazine, used in burn patients. Serum Cu concentration has also been reported to be decreased for approximately 2 weeks post-burn with normal or increased ceruloplasmin levels.¹⁵³ Cu levels in the urine begin to increase as early as 5 days after burn injury,^{153,154} with urinary copper levels reaching the highest concentrations between days 11 and 17 after injury.^{19,154} As much as 20 - 40% of the body's Cu content is lost during the first 7 days after burn injury.¹⁴⁹

Similar to Zn, Cu deficiency may develop in critically ill or injured patients due to excessive gastrointestinal losses,¹⁴⁷ high cutaneous losses (burns)¹⁴⁹ and increased urinary copper excretion.¹⁴⁸

Selenium

In both acute¹⁵⁵⁻¹⁵⁷ and chronic¹⁵⁸ illnesses, the plasma concentration of Se decreases in proportion to the magnitude of the inflammatory response.

Se concentrations follow a similar pattern to the described changes in serum plasma trace element concentrations in the presence of the acute phase reactants. Se concentrations decrease by 10% at day 1 following minor surgery, followed by a subsequent increase toward the preoperative concentration by day 6 postoperatively.¹⁵⁹

Low plasma Se concentrations have been described in a variety of clinical conditions such as myocardial infarction, severe burns,¹⁶⁰ acute pancreatitis, cancer¹⁵⁸ and in intensive care patients.¹⁵⁵ Studies in thermally injured patients¹⁶⁰ have demonstrated decreased serum Se concentrations, essentially throughout the course of hospitalisation, with slightly elevated urinary losses on days 3 - 7 post-injury. Hunt *et al.*¹⁶¹ demonstrated decreased erythrocyte glutathione peroxidase activity in thermal injury, which supports the concept of true Se deficiency instead of merely a decrease in its carrier proteins.

It has been proposed that the aetiology for the observed decrease in serum Se levels in thermal injury is multifactorial and may include a manifestation of the APR, drug toxicity (through oxidative stress mechanisms),¹⁶² a decreased red blood cell survival rate that is often observed in thermal injury¹⁶³ and/or an antagonistic relationship with silver.^{160,164}

CHANGES IN PLASMA CONCENTRATIONS OF VITAMINS DURING THE APR

Vitamins are organic compounds that are essential for normal growth and maintenance of body functions, playing key roles in many different metabolic processes both in health and disease. Vitamins thus play an important role in critical illness, in which hypermetabolism, healing and immune function is so essential for survival. A deficiency state, which can occur readily, will clearly amplify the magnitude of the disease.^{165,166} Although normal requirements for the healthy population have been established,^{167,168} little is known about vitamin requirements in the critically ill patient.

It has been documented that vitamin requirements are increased in conditions such as stress (vitamins B₂, B₆, C and pantothenic acid), immune system dysfunction (vitamins A, D, E, B₆, C, pantothenic acid and folic acid), wound healing (vitamins A, B₂, and C) and prevention of free radical/peroxidative injury (vitamins C and E). Additionally, many drugs have been shown to increase vitamin requirements. Varying degrees of malabsorption must also be considered in the critically ill.¹⁶⁹

The increased metabolic rate and catabolism associated with the APR are thought to increase the requirements of such micronutrients as vitamins A, E, B₆, C, D and folate. Indeed, a significant decrease in blood concentrations of vitamin A, E, B₆ and C (leucocytes)¹⁰⁷⁻¹⁰⁹ and vitamin D¹⁰⁷ have already been documented.

Louw *et al.*¹⁰⁷ demonstrated transient, but significant, decreases in the concentrations of leucocyte vitamin C, and in plasma concentrations of vitamin A, retinol-binding protein (RBP), vitamin E, total lipids, pyridoxal-5'-phosphate and albumin in their longitudinal study investigating blood vitamin concentrations during the APR. Blood concentrations of pyridoxal-5'-phosphate, RBP and leucocyte vitamin C decreased to values below the respective normal ranges but normalised without any therapeutic interventions. The transient and self-correcting nature of the decreased values argues against a true deficiency state, although it must be noted that the APR in this study population was of a short duration.

The mechanism by which these changes are brought about is not clear, but is almost certainly multifactorial and possibly mediated by, and occurs in response to, the APR. Various factors could contribute to a decrease in measured vitamin levels. The APR has a profound influence on protein, carbohydrate and lipid metabolism and also affects fluid distribution with resultant fluid volume changes in the injured host.^{6,170} These factors alone may influence the measured concentrations of certain vitamins as may extended periods of fasting.⁸

The APR also induces changes in carrier protein status, and indeed a reduction in the concentrations of albumin, RBP and

pre-albumin were reported in the study by Louw *et al.*,¹⁰⁷ possibly contributing to the changes observed in vitamin A and pyridoxal-5'-phosphate concentrations. The redistribution of fluids, characteristic of the APR, could affect measured vitamin levels directly, or may affect these values by redistribution of their carriers.

An increased demand for certain vitamins can be postulated during the APR, since the vitamins, which have been reported to decrease in blood/serum concentration, represent metabolically important substances in supporting a number of biochemical functions during the APR. For instance, the role of vitamin B₆ in protein metabolism is well known and the demand for the antioxidant vitamins E and C might be increased due to its role in the defence of the host against oxidant damage.¹⁷¹ Furthermore, increased urinary losses of riboflavin and vitamin C may occur in conjunction with negative nitrogen balance.¹⁷² Vitamins are also known to participate in metabolic processes activated during host defence mechanisms.¹⁷³ The B-group vitamins, vitamin C and folate all participate in the metabolism of activated phagocytic cells. Additionally vitamin C is recognised for its importance in the locomotive activity of phagocytic cells, as well as its contributions to the immune system.¹⁷⁴

Vitamin A

During infections (especially those associated with fever and a systemic APR) plasma retinol can decrease to as low as about a third of its concentration in the same individual when healthy.¹⁷⁵⁻¹⁷⁷ However, during the recovery phase from the illness, plasma retinol characteristically returns to normal within a time course of 1 - 2 weeks,^{175,178} arguing against a deficiency state. It is known that plasma retinol concentration, on its own, should not be used as an indicator of vitamin A status in the presence of infections. Although concomitant assessment of plasma acute phase proteins (specifically CRP, serum amyloid A, 1-antichymotrypsin and 1-acid glycoprotein) has been proposed,¹⁷⁹⁻¹⁸¹ there remain significant limitations in terms of defining the contribution of infection to decreased plasma levels and also in the interpretation of efficacy data from intervention.¹⁸² Further research is required to identify reliable methods to determine plasma retinol concentrations under these conditions.

Several mechanisms have been proposed to explain the lowering of plasma retinol during illness: decreased liver secretion of the retinol-RBP complex, loss of the complex to the extravascular space,¹⁸³ increased loss in the urine^{184,185} and the uptake of retinol by tissues involved in the immune response or in tissue repair.¹⁸² This would imply that the decrease in retinol might actually be a beneficial adaptation. Although perhaps beneficial in the short term, in severe or prolonged illness, increased retinol demand or urinary retinol losses could potentially deplete vitamin A stores.^{184,185}

Antioxidant vitamins

Reactive oxygen species (ROS) are constantly produced in humans under normal circumstances. Protective antioxidant systems help defend against ROS-induced cellular damage. Oxidative stress is thought to increase in the presence of the APR because of the accompanying activation of neutrophils and the subsequent release of free radicals,¹⁸⁶ which may overwhelm defensive mechanisms and disturb the prooxidant-antioxidant balance in favour of the former, leading to potential damage.¹⁸⁷ Oxidative stress can cause lipid peroxidation, damage to DNA, and cell death,¹⁸⁸ and has been associated with sepsis, shock, mechanical ventilation, organ dysfunction, adult respiratory distress syndrome (ARDS) and surgery.¹⁸⁹ In general, serum antioxidant vitamin concentrations decrease, and measures of oxidative stress increase in critically ill patients. Recently, Oldham *et al.*¹⁸⁷ demonstrated a decrease in plasma antioxidant concentrations from the first day following trauma (when compared with controls), but the decrease became negligible (except for γ -tocopherol and lycopene concentrations) when the plasma antioxidant concentrations were individually adjusted for plasma total cholesterol concentrations. This reported decrease therefore could largely be attributed to haemodilution and changes in plasma cholesterol concentrations as the result of trauma, emphasising the importance of taking these factors into account when evaluating antioxidant plasma concentrations.

Boosalis *et al.*¹⁹⁰ demonstrated a significant decrease in the plasma concentrations of lycopene, alpha carotene, beta carotene and total carotenoids in a subgroup of elderly women suspected of experiencing chronic low-grade inflammation (responsible for the induction of the APR). Previously these authors also observed a decrease in the circulating levels of vitamin C after traumatic injury.

Antioxidant status and lipid peroxidation have also been studied in patients with sepsis and multisystem organ failure.¹⁹¹ Plasma concentrations of α -tocopherol were significantly lower in patients than in healthy control subjects, while beta carotene and lycopene concentrations were decreased below the respective reference ranges. Furthermore, Borrelli *et al.*¹⁹² measured daily plasma concentrations of ascorbic acid and α -tocopherol as predictors of multisystem organ failure in intensive-care patients. Plasma ascorbic acid concentrations were significantly lower in the patients who developed multisystem organ failure, although α -tocopherol levels were not significantly different. Whether of course serum ascorbic acid can be used as a tool to predict the development of multisystem organ failure in patients at risk remains to be confirmed.

In surgical patients, Agarwal *et al.*¹⁹³ studied the serum concentrations of ascorbic acid and the tocopherols in 57 surgical patients. All vitamin concentrations decreased significantly on day 1 after surgery, with a maximal decrease

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by day 3 post-surgery (41% in ascorbic acid, 27% in α -tocopherol, 31% in γ -tocopherol). Vitamin concentrations had returned to normal by day 7 after the operation. A subgroup of patients with postoperative infections had significantly lower preoperative concentrations of α -tocopherol. Lower preoperative concentrations of α -tocopherol and γ -tocopherol were significantly related to death in the 6 patients who died during the course of the study.

Similarly low concentrations of α -tocopherol, retinol and all carotenoids have also been reported in children with severe malaria.¹⁹⁴ Using multivariate analysis it was determined that cholesterol was the most significant factor explaining the variance in α -tocopherol (29%) whereas RBP was responsible for 95% of the variance in retinol. The authors conclude that low plasma lipid-soluble micronutrient concentrations in malaria are strongly influenced by the reduction in their carrier molecules, which, in turn, are low as a consequence of the APR.

The available literature is confirmatory of significant changes in the serum concentration of a number of vitamins in the presence of the acute phase response and that the decrease in serum levels appears to normalise spontaneously, at least in the short term, when the acute phase response subsides. It would be of obvious importance to know whether these noted decreases in vitamin levels reflect true deficiency states at the tissue level, or whether they merely represent a transient adaptive response. The transient and self-correcting nature of the decreased values when the APR was of a short duration argues against a true deficiency state. However, if low vitamin concentrations persist during a prolonged APR,^{195,196}

supplementation may become important in order to overcome the potentially detrimental effects of vitamin deficits on the host's metabolism.

MICRONUTRIENT SUPPLEMENTATION

In practical terms, vitamin supplementation of these patients is generally accepted to be of importance and the several reports of vitamin deficiencies among hospitalised patients, despite the daily provision of vitamins in nutritional support regimens,^{195,197} attests to the wisdom of this approach. Current recommendations indicate the daily administration of at least the Recommended Dietary Allowance (RDA) for vitamins, minerals and trace elements in the seriously ill (Tables IV and V), hypermetabolic patient.^{9,198} Guidelines for parenteral vitamin therapy are available¹⁹⁹ and although these are based on the RDAs for normal people, they attempt to take into account the possibility of increased requirements due to the underlying disease process. However, some studies have shown that these supplements may be inadequate.^{196,200} In this regard, a number of studies have been conducted with the aim of not only defining micronutrient requirements in the acutely ill but also documenting benefits in terms of clinical outcomes.

Trace elements

The importance of trace element supplementation in the acutely ill patient is probably best exemplified by a carefully conducted, prospective study¹⁵³ which documented that supplementation with larger than the currently recommended

Table IV. Recommended daily vitamin requirements (adults \geq 19 years)*

	Enteral dose		Parenteral dose AMA (1975) ¹⁹⁹
	RDA (1989) ¹⁶⁷	DRI ¹⁶⁸	
Fat-soluble vitamins			
Vitamin A	800 - 1 000 μ g RE	—	3 300 IU
Vitamin D	5 - 10 μ g	5 - 15 μ g [†]	200 IU
Vitamin E	8 - 10 mg α -TE	—	10 IU
Vitamin K	60 - 80 μ g	—	0.5 mg
Water-soluble vitamins			
Vitamin B ₁ (thiamin) (mg)	1.0 - 1.5	1.1 - 1.2 [‡]	3
Vitamin B ₂ (riboflavin) (mg)	1.2 - 1.7	1.1 - 1.3 [‡]	3.6
Niacin (mg)	13 - 19	14 - 16 [‡]	40
Vitamin B ₆ (pyridoxine) (mg)	1.6 - 2.0	1.3 - 1.7 [‡]	4
Vitamin B ₁₂ (cyanocobalamin) (μ g)	2	2.4 [‡]	5
Vitamin C (ascorbic acid) (mg)	60	—	100
Folic acid (μ g)	180 - 200	400 [‡]	400
Biotin (μ g)	30 - 100 [§]	30 [†]	60
Pantothenic acid (mg)	4 - 7 [§]	5 [†]	15

*Excluding pregnant and lactating women.

[†]Adequate intake (AI).

[‡]RDA.

[§]Estimated safe and adequate daily dietary intake.

RDA = recommended dietary allowance, DRI = dietary reference intake, AMA = American Medical Association.

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Table V. Recommended daily trace element requirements (adults ≥ 19 years)*

	Enteral dose		Parenteral dose	
	RDA (1989) ¹⁶⁷	AMA (1979) ²²³	AMA (1979) ²²³	Shenkin ²²⁴
Iron (mg)	10 - 15	Not stated		1.1
Zinc (mg)	12 - 15	2.5 - 6.0		6.4
Copper (mg)	1.5 - 3.0 [†]	0.5 - 1.5		1.3
Iodine (µg)	150	Not stated		130
Manganese (mg)	2.0 - 5.0 [†]	0.15 - 0.8		0.27
Fluoride (mg)	1.5 - 4.0 [†] (3 - 4 mg) [‡]	Not stated		0.95
Chromium (µg)	50 - 200 [†]	10 - 15		10
Selenium (µg)	55 - 70	Not stated		200
Molybdenum (µg)	75 - 250 [†]	Not stated		20

* Excluding pregnant and lactating women.

† Estimated safe and adequate daily dietary intake.

‡ Dietary reference intake (DRI), 1997¹⁶⁸; adequate intake (AI).

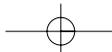
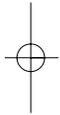
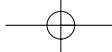
RDA = recommended dietary allowance, AMA = American Medical Association.

doses for Zn, Cu and Se had a significant and beneficial effect on recovery after major burns (41% of body surface). One group of patients received trace element (Zn, Cu, Se) supplements according to current recommendations, while the test group of patients received higher dose supplements of the same trace element (40 mg Zn, 4.5 mg Cu and 190 µg Se), which were sufficient to meet increased requirements due to cutaneous losses (as a result of severe burns) and to normalise plasma concentrations. The treatment group had a significantly higher increase in leucocyte counts (mainly neutrophils), a significantly shorter overall hospital stay (57 v. 45 days, respectively) and a shorter overall hospital stay in relation to per cent burn surface (1.6 v. 1.1 days/% burns, respectively). While the mechanism(s) underlying these favourable clinical outcomes remains to be elucidated, available data²⁰¹ would support the concept that improvements in immune function following the high dose trace element supplements may have been important in attaining the described outcomes. In this regard a more recent placebo-controlled trial studied the clinical and immune effects of trace element supplements in major burns (48% of body surface).²⁰² Again one group of patients consumed standard trace element intakes (Zn, Cu and Se) while the treatment group received the standard intake plus additional Zn, Cu and Se supplements (406 µmol, 40.4 µmol and 2.9 µmol respectively) for 7 days after injury followed by the standard intake thereafter. Total leucocyte counts tended to be higher in the treatment group because of higher neutrophil counts. Additionally, the number of infections per patient was significantly lower in the treatment group because of fewer pulmonary infections. The authors conclude that early trace element supplementation appears to be beneficial after major burns since it significantly decreases the number of bronchopneumonia infections and is associated with a shorter hospital stay when data were normalised for burn size.

Physiological selenium replacement in patients with severe SIRS has been studied in a randomised, prospective pilot study²⁰³ based on the observation that selenium levels are lower in patients with severe illness. The treatment group, receiving high-dose selenium supplements, showed rapid normalisation of plasma selenium concentrations and the APACHE III score was significantly reduced when compared with the control group. Additionally, the requirement for haemodialysis was significantly lower in the treatment group.

In a trial of zinc supplementation involving closed head injured patients, the treatment group documented significantly reduced mortality, and mean Glasgow Coma Scores were significantly better on days 15 - 28 when compared with the control group.²⁰⁴ Zn supplementation has been associated with striking reductions in diarrhoea and improvements in mucosal functions.²⁰⁵ Additionally, supplementation with low doses of Zn and Se significantly reduced infectious events in the institutionalised elderly.²⁰⁶

On the other hand, it has been suggested that Zn supplementation to correct Zn concentrations may be harmful in terms of inducing more severe infections²⁰⁷ and of increasing the level of fever in patients on total parenteral nutrition therapy, who were admitted for catheter sepsis or pancreatitis,²⁰⁸ thereby resulting in an exaggerated APR. Similarly, other studies have documented that iron replacement therapy increases the risk of severe infections as well as mortality in both humans and animals and confirms the protective effects of hypoferraemia against injury and infection.^{150,209,210} Fe replacement therapy can in fact predispose to infectious complications and death in stressed patients.²⁰⁹ Indeed it is thought that Fe supplementation may activate latent infections,²¹¹ result in more adverse outcomes to infections¹²⁷ and thereby have an adverse effect on health, especially in developing countries.²¹²



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Vitamins

It is increasingly realised that catabolic disease may alter the requirements for specific nutrients; thus, the administration of required substrates might greatly facilitate a patient's anabolic response to a life-threatening disease. In this regard, it is known that, in man, dietary supplementation with ascorbic acid, tocopherols and vitamin B₆ enhances a number of aspects of lymphocyte function,²¹³ which could have a direct effect on the extent and duration of the APR. There is some evidence that supplementary vitamin C may accelerate wound healing in the absence of clinical deficiency.²¹⁴ Indeed, in the case of vitamin C and pantothenic acid in relation to wound healing a dose response relationship has been reported.²¹⁵ Furthermore, vitamin supplementation has been reported to improve wound healing²¹⁶ and to lead to an increase of Mg, Cu and Mn levels in tissues, and, concomitantly, to a decrease in Fe levels. Experimental studies have also shown that supplementation with vitamins C, E and A improved survival in burn injury.²⁵

Enteral feeding of critically ill patients with a formula supplemented by pharmacological amounts of vitamins A, C and E improved low density lipoprotein resistance to stress, but had no effect on clinical outcomes.²¹⁷ However, other recent studies evaluating alpha-tocopherol supplementation demonstrated no impact either on oxidative stress or clinical benefit,²¹⁸ or any alteration in lipid peroxidation.²¹⁹

In relation to immune function, Maderazo *et al.*²²⁰ demonstrated that antioxidant therapy (ascorbic acid and α -tocopherol) significantly improved the neutrophil locomotory dysfunction in blunt trauma. Since improved bacterial defence may be reasonably assumed to occur following the restoration of impaired neutrophil function, one can speculate that antioxidant therapy might have an impact on infection and mortality rates in seriously injured patients.

Other vitamins of importance in terms of supplementation include vitamin K and the B group of vitamins. Vitamin K deficiency can develop rapidly in critically ill patients who are kept nil per mouth, have decreased biliary excretion or are on broad-spectrum antibiotics.¹⁷ Additional vitamin K supplementation may be necessary in such patients, since not all intravenous (IV) multiple vitamin supplements contain this vitamin.¹⁹⁸ Water-soluble vitamins, which are stored in limited amounts and are depleted quickly with starvation, should also be supplemented early in the course of sepsis.¹⁹⁸ Thiamin deficiency should be anticipated in cases where a carbohydrate-rich feeding regimen is employed, when prior malnutrition is known or suspected, in patients with sepsis and in patients with a history of alcohol abuse.¹⁷

The currently available evidence indicates that the micronutrient requirements of the critically ill patient remain largely undefined. Whether restoration of the consistently decreased serum/blood concentrations during the acute phase

response to normal is helpful, harmful or of no consequence, depending on the clinical setting, is still largely unknown. Nevertheless, emerging evidence regarding the potential of any such supplements in influencing clinical outcomes is encouraging. Nutrition support practitioners considering such supplements in critically ill patients should proceed with caution and consider the amounts of such micronutrients a patient is already receiving through an oral diet and/or enteral/parenteral nutritional support. In the case of antioxidant supplements, it should be borne in mind that the available data in critical illness do not, at present, support pharmacological use of these compounds and that the potential for creating a pro-oxidant micro-environment may have as much potential for harm as for benefit in the well-nourished patient. Furthermore, caution should be exercised with any supplements in the presence of renal impairment, especially of supplements containing fat-soluble vitamins and trace elements.^{221,222} Until formal clinical trials have defined the potential benefits and/or adverse effects of micronutrient therapy, relatively conservative supplementation protocols together with astute interpretation of clinical and biochemical indices of micronutrient nutriture are recommended. Additionally, the nutritional status of the patient, together with the type and duration of injury should be considered before proceeding with any supplementation. In practical terms and within the South African context, the most prudent approach to micronutrient supplementation in these patients should include the daily provision of micronutrients using the currently available intravenous preparations of micronutrient supplements in the country, with the additional daily provision of 250 mg of vitamin C. Clinical experience has shown this approach to be effective in preventing overt clinical deficiency syndromes and to be free of any adverse effects. Further research is imperative so that selective micronutrient therapy can be initiated as early and safely as possible.

CONCLUSION

Nutrition support in the hospitalised patient is vitally important in terms of providing all essential nutrients, preventing nutrient deficiencies and attenuating catabolism. This is even more important in the critically ill, hypermetabolic patient, who characteristically presents with a greater disease severity and attendant complications. An adequate provision of macro- and micronutrients is necessary for maintenance of an optimal nutritional status during the APR in order to promote wound healing and prevent malnutrition-related complications. It is therefore imperative that the nutrition support practitioner has an understanding of the metabolic response to injury and is aware of the effects of the APR on macro- and micronutrient status so as to intervene effectively with specialised nutritional support. In contrast to the considerable body of knowledge regarding the effect of the

APR on macronutrient status, knowledge on micronutrient status and requirements is limited and in need of further investigation, especially in the critically ill patient. Further studies are needed, especially studies designed to define clinical outcomes in relation to levels of micronutrient provision and biochemical indices of micronutrient status.

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CONTINUING PROFESSIONAL DEVELOPMENT ACTIVITY FOR DIETITIANS
SAJCN CPD activity No 17 - November 2002

You can obtain 3 CPD points for reading the article: "Metabolic and nutritional consequences of the Acute Phase Response" and answering the accompanying questions.
 This article has been accredited for CPD points for dietitians. (Ref number: DT 02/3/277/12)

HOW TO EARN YOUR CPD POINTS

1. Check your name and HPCSA number.
2. Read the article and answer all the questions.
3. Indicate your answers to the questions by coloring the appropriate block(s) in the cut-out section at the end of this questionnaire.
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5. Make a photocopy for your own records in case your form is lost in the mail.
6. Send the cut-out answer form by mail, NOT BY FAX to: SASPEN Secretariat, SAJCN CPD activity No 17, c/o Department of Human Nutrition, PO Box 19063, Tygerberg, 7505 to reach the office not later than 31 January 2003. Answer sheets received after this date will not be processed.

PLEASE ANSWER ALL THE QUESTIONS
 (Mark the ONE correct choice)

- | | |
|---|---|
| <ol style="list-style-type: none"> 1. Metabolism in the critically injured patient is primarily aimed at limiting energy expenditure and conserving visceral nitrogen.
 [a] True
 [b] False 2. After injury, a reprioritisation of protein synthesis occurs which leads to a significant increase in the serum concentration of acute phase proteins due to an increase in hepatic synthesis.
 [a] True
 [b] False 3. Metabolism during the acute phase response (APR) consists of an interaction between biochemical mediators, the neuro-endocrine response to trauma and a decrease in the intake of nutrients.
 [a] True
 [b] False 4. Cytokines are responsible for the alterations seen in energy expenditure, gluconeogenesis, lipolysis, vascular permeability and skeletal muscle proteolysis in the critically injured patient.
 [a] True
 [b] False 5. Interleukin 1 (IL-1) and tumor necrosis factor (TNF-∞) are primarily immunosuppressive and counter-inflammatory.
 [a] True
 [b] False 6. It would appear that the individual level of synthesis of either pro- or anti-inflammatory cytokines alone might be a more predictive determinant of clinical outcomes than the ratio of the two.
 [a] True
 [b] False | <ol style="list-style-type: none"> 7. The post-injury period is characterised by a decrease in glucose turnover, thereby optimising host defences and ensuring wound repair.
 [a] True
 [b] False 8. In severe sepsis and, to a lesser extent, trauma there is a blunting of the adaptive ketonaemic response and its subsequent nitrogen conservation.
 [a] True
 [b] False 9. During the APR, a redistribution in plasma trace elements occurs with a decrease in the concentrations of iron (Fe) and copper (Cu) and a concomitant rise in zinc (Zn) levels.
 [a] True
 [b] False 10. The increased metabolic rate and catabolism associated with the APR are thought to increase the requirements of such micronutrients as vitamin A, E, B₆, C, D and folate.
 [a] True
 [b] False 11. Plasma ascorbic acid concentrations have been investigated as a possible tool to predict the development of multisystem organ failure in patients at risk.
 [a] True
 [b] False 12. High dose Fe supplementation is beneficial to all critically ill patients by reducing infectious complications and thus mortality risk.
 [a] True
 [b] False |
|---|---|

 ✂ Cut along the dotted lines and send to: SASPEN Secretariat, SAJCN CPD activity No 17, c/o Department of Human Nutrition,
 PO Box 19063, Tygerberg, 7505 to reach the office not later than 31 August 2002

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Full member of ADSA: |_| yes |_| no If yes, which branch do you belong to? _____

Full member of SASPEN: |_| yes |_| no Full member of NSSA: |_| yes |_| no

"Metabolic and nutritional consequences of the Acute Phase Response"

J Visser, D Labadarios

Please color the appropriate block for each question

(e.g. if the answer to question 1 is a: 1) a b)

- | | | | |
|--|---|---|---|
| 1) <input type="checkbox"/> a <input type="checkbox"/> b | 2) <input type="checkbox"/> a <input type="checkbox"/> b | 3) <input type="checkbox"/> a <input type="checkbox"/> b | 4) <input type="checkbox"/> a <input type="checkbox"/> b |
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