.....INTRODUCTION

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When faced with any situation that inflicts harm to the well being of the organism its body initiates a cascade of physiological responses designed to maximize the chances of survival. This complex interaction of various organ systems is common to much injurious process such as sepsis, trauma and even surgery.

The study of metabolic response to injury has its root in the observation made by Jhon Hunter as early as in 1794. He mentioned that "there is a circumstance in attending accidental injury, which does not belong to disease, viz; that the injury done in all cases a tendency to produce the disposition and means of cure". Yet a century passed before the great German pathologist established the scientific basis of cell-pathology. The influence of German pathology led the American pathologist and medical statesman Welch (1937), to emphasize the frequently inadequate adaptations of tissues to disease an injury. This was in contrast to statement of Canon (1939), who extended the concepts of Bernad to stress on the homeostatic mechanisms by which the body would adapt to various insults. In the early 1930's Cuthbertson reported that the skeletal injury results in an increase excretion of nitrogen and other intracellular costituents, hilighting the importance of negative nitrogen balance. During 1950-1960's Moore (1959) extended the use of metabolic balance

studies by adding measurements of body composition and hormone level to establish modern standards of surgical metabolism and endocrinology. Hunter (1794) and Kinney (1992), mentioned that there is an increase in resting energy expenditure (REE) in hospitalized surgical patients, patients with multiple fracture and febrile patients with systemic infections. Further studies have shown that the increase in REE was the result of hypermetabolism occurring in this group of patients, which includes proteolysis and increased nitrogen excretion, mobilization of fat stores and subsequently oxidation of fatty acids in liver. Both these processes contribute for synthesizing carbohydrate substrates (Kinney *et al.*,1983; Wolfe *et al.*,1985). During 1970-1980's the focus was on regulation of the fore mentioned metabolic changes by various endocrine systems. Various counter-regulatory hormones have been considered responsible for stress response (Cuthberston, 1945). The interplay between central nervous system and endocrine organs was held responsible for various metabolic changes (Wernerman *et al.*, 1985; Wolfe *et al.*, 1985). In the past decade, the studies were concentrated on the role of inflammatory mediators in the metabolic consequences during acute biological stress. The substantial evidences suggest that the endogenous inflammatory and immuno modulating cytokines, in particular, tumor-necrosis factor (TNF), interlukin-1 (IL -1) and interferon (ϒ) are the main substances working behind the metabolic response to stress (Boujoukos *et al.*, 1993; Fong *et al.*, 1994).

The current care of critically ill patients is the result of particular steps taken in the development of hospital care. Growing attention to shock and circulatory failure led to blood banking during world war II, just as renal failure led to hemodialysis in the following decade. The turbulent decade of 1960's saw the introduction of intensive care units with steady improvement

in both monitoring and vital organ support. In parallel fashion, growing recognition of weight loss in the critically ill led to efforts to provide intravenous nutrition and ultimately, to the introduction of total parental nutrition (TPN) in 1960's. Total parental nutrition proved to be more than a new and important therapy; it was a powerful research tool for extending our understanding of the metabolic response in the critically ill patients (Kinney, 1995).

In the present days, the research work is directed towards controlling the incidence of morbidity and mortality in intensive care units.

METABOLIC RESPONSE TO INJURY AND CRITICAL ILLNESS

Injury may be defined as an adverse influence, external or internal, on the cell which deranges the cell's ability to maintain a steady normal or adapted homeostasis. The steady state is in fact a fluid range within which the cell oscillates and is capable of optimal functions. The causes of cell injury and death ranges from the gross physical violence of an automobile accident to the subtle genetic lack of vital intracellular enzyme which impairs normal metabolic functions. Factors that induce injury are; hypoxia, physical injury, chemical injury, biological agents, immune mechanism, genetic defects, malnutrition (Robbins, 1989)

GENERAL FEATURES OF THE RESPONSE TO INJURY

EBB PHASE

In a series of observation first made more than 50 years ago and repeatedly confirmed in the essential details, Cuthbertson noted that patients with uncomplicated trauma, such as long bone fracture, demonstrate characteristic clinical and laboratory findings during recovery. Immediately after injury and

persisting for 24 hours is a period of "diminished circulatory vitality", the Ebb Phase termed by Cuthbertson. It is now well known that these early systemic changes following trauma results primarily from a decreased cardiac output that attends hypovolemia from blood loss or extravascular fluid sequestration. Oxygen consumption is decreased typically in ebb phase, in most instances owing to inadequate oxygen transports to the tissues. Body temperature tends to be subnormal. There is both clinical and laboratory evidence of intense activation of the sympathetic nervous system and the hypothalamo-pituitary-adrenal axis. The resultant accompaniment is an elevated serum glucose concentration, while serum insulin levels tends to become subnormal and the levels of circulating catecholamines are elevated. The elevated lactate and free fatty acid levels are also a sequel to these hormonal disturbances.

FLOW PHASE

As Cuthbertson originally noted, elevations of body temperature, respiratory rate, and pulse rate are consistently observed by the latter part of the first week after injury. Cardiac output by then has returned to normal range and is accompanied by hypervolemia or normovolemia (volume of circulatory fluid-blood). The cardiac output characteristically continues to increase, reaching a plateau in supernormal range by the end of second week. Barring specific complications, regional blood flow to viscera, particularly to kidney and liver is also elevated, as is flow to the region of the wound. Weight loss begins to become apparent at this time. Whole body resting oxygen consumption tends to rise to a plateau during two weeks after injury. Nitrogen excretion is also increased to a far greater extent than can reasonably be attributed to local tissue breakdown at the injury site. Cuthbertson correctly deduced that

increased urinary nitrogen, sulfur, and phosphorous losses were manifestations of a generalized increase in the muscle protein catabolism and not simply a consequences of resorption of injured or necrotic tissue. The increase in resting metabolic rate, which occurs in the presence of minimal or decreased caloric intake, necessitates the utilization and oxidation of body's own fuel reserves.

During this phase blood glucose is normal or elevated and tolerance to exogenous carbohydrate is decreased- 'diabetes of injury' (Black, *et al.*,1982). The rate of gluconeogenesis is accelerated ; glucogenic amino acids (released primarily from skeletal muscle) are utilized as a substrate for the formation of new glucose. Serum insulin levels become normal or elevated ; circulating glucagon is dramatically increased. Superimposed stress such as surgical procedures or infections frequently exacerbate the al-readily increased metabolic demands. Adipose tissue lipids, the major fuel reserve is mobilized and oxidized after injury, but less preferentially than in starvation.

STARVATION: AN ADAPTIVE RESPONSE

Although patients develop critical illness early following trauma and shock, noninjured or minimally injured patients may also become critically ill. In these cases especially, the acute metabolic effects of critical illness are frequently superimposed on a preexisting state of either short-term or long-term starvation, an often unrecognized phenomenon that occurs in a high proportion of hospitalized patients (Mullen *et al.,* 1979; Steffee., 1980). In contrast to the hypermetabolism of critical illness, starvation is an adaptive mechanism designed to maintain euglycemia in the absence of caloric intake while meeting the metabolic requirements of functioning tissues and conserving protein stores (Cahill ,1970; Levenson *et al.*,1983). These effects are readily reversible with

simple re-feeding. The metabolic changes of starvation serve to meet the continued energy demand of the brain, renal medulla, hematopoetic tissues, and other metabolically active organs. The production of glucose from liver and muscle glycogen stores depletes those stores rapidly-typically within 12-24 hours and alternative sources of energy must be used. Protein stores are next to be broken down, at a rate of up-to 120-140g/day to meet the large glucose requirements of such tissues as the brain. If this high rate of protein breakdown continued it would result in over-depletion and death. However, during period of fasting longer than 5-7 days, the primary fuel source shifts from protein to fat (major fuel reserve). The ketone bodies, acetoacetate and β-hydroxybutyrate, replace glucose as the primary metabolic substrates for the brain. Brain glucose use is markedly diminished with partial recycling of glucose through Cori Cycle. Gluconeogenesis may develop in kidney with a direct effect on the maintenance of acid-base status by the generation of ammonia. Insulin level remains low to facilitate the mobilization of fat and protein reserves. Free fatty acid becomes the primary fuel source whereas amino acids are used for protein synthesis. Simple starvation can usually be tolerated without appreciable morbidity for 4-6 day postoperatively in previously well-nourished patients. However, the increase in catecholamine concentration after surgery or following injury inhibits the metabolic adaptation to starvation. Consequently, the patient who is stressed and is unable to adapt to the additional stress of starvation, often requires early and aggressive exogenous nutritional support.

INTERMEDIARY METABOLISM IN CRITICAL ILLNESS:

PROTEIN

Although proteins within the body cell mass are constant in amount, a dynamic flux exists for individual protein which results in an equilibrium between ongoing

synthesis and breakdown (Kinney *et al.*, 1983). Enterally or parenterally acquired amino acids as well as endogenous amino acids derived from protein breakdown contribute to protein synthesis. In normal healthy adults about 350g protein is synthesized daily, which usually matches protein breakdown, so that lean body mass remains constant within fairly narrow limits. Since dietary protein is normally about 75g/day, it is obvious that endogenous amino acids derived from protein catabolism are re-utilized for protein synthesis to a significant extent. Net protein losses can therefore result from either net reduction in rate of synthesis or acceleration of proteolysis. An abrupt increase in protein synthesis occurs after injury, especially in liver and bone marrow. Increased concentration of several circulating acute phase reactants and related compounds can be measured e.g. C-reactive protein and α-acid glycoprotein level may increase 20 folds. Fibrinogen, haptoglobin and other molecules have an increased rate of synthesis and a presumed survival benefit following injury. Thus from a teleological point of view, fibrinogen improves clotting efficiency; haptoglobin prevents renal injury by binding hemoglobin; complement is important in the immune response; increased synthesis of a variety of white blood cells presumably aids immunoreactivity; and increased rate of cell proliferation in the wound are necessary for wound healing. Liver alanine content acutely increases by as much as three times that before injury and serves as substrate for both acute phase reactant and gluconeogenesis.

In skeletal muscles, protein catabolism predominates. Subsequently an increased net release of urinary urea nitrogen loss is observed. These amino acids are subsequently used in part by the viscera for protein synthesis and gluconeogenesis. Uptake by the viscera of amino acids released from skeletal muscle exceeds their production rate from muscle so that plasma levels of

many amino acids are typically reduced. This graded and complex metabolic adaptation in muscle leads to muscle atrophy and weakness and would seem to be deleterious; whereas the protein metabolic response in liver appears to be beneficial.

There is considerable evidence that the response of muscle is not heterogeneous. Many differences have been observed in metabolism of muscle from animals subjected to different types of trauma, and individual muscle from the same animal may react differently (Tischler *et al.*, 1983; Downey *et al.*, 1986). It appears likely that the biochemical composition and physiological function of individual muscle are significant determinants of their response to injury.

When protein dynamics in incubated intact rat epitrochlear and soleus muscles following graded injury (Downey *et al.*, 1986) (the epitrochlearis muscle is so called fast-twitch, white-fiber muscle that functions intermittently to change limb position; the predominantly red-fiber soleus is important in posture maintenance) was measured, an increased metabolic rate of about 15% in the least severely injured animals was observed and approximately 40% in more severely stressed animals. Protein synthesis rate were not significantly altered except for increase in directly injured muscles. The relationship between catabolism in both the general protein pool and the myofibrillar protein was found to be complex.

The protein population of the white fiber epitrochlearis was considerably more labile in response to post-traumatic catabolic stimuli than were the same protein population in the predominantly red-fiber soleus. Both the contractile proteins and to a lesser extent the mixed protein pool of epitrochlearis evidenced this property. However, tyrosine release was not significantly

elevated but to a lesser extent than in the epitrochlearis. Thus the protein constituents of a given muscle do not necessarily respond similarly. The liability of myofibrillar proteins in the white fiber epitrochlear exceeds that measured in red fiber soleus at both levels of injury severity tested. Other investigators have also seen protein liability in fast-twitch muscle and an accentuated response of myofibirillar protein breakdown in response to other catabolic stimuli such as starvation and sepsis (Hasselgren *et al.* , 1989). Thus, muscles involved in intermittent activity and contractile proteins, actin and myosin appears to be the most severely affected by critical illness. Similar phenomena may play a role in the development of the weakness and debility in patients who have undergone critical illness.

Cuthbertson (1930) was one of the first to conclude that the increased nitrogen loss following injury reflects not only a generalized increase in the breakdown rate of skeletal muscle but also other factors, especially inactivity. He estimated that as much as 40% of the increase nitrogen loss was due to disuse atrophy (Cuthbertson, 1945). Studies of Deitrick *et al.,* (1948), demonstrated that normal subjects receiving an otherwise weight-maintaining diet develop negative nitrogen balance when immobilized in spica casts. Active muscle contraction (and even passive manipulation), can reduce this source of nitrogen loss during critical illness. Thus, exercise and physical therapy even on limited scale in critical ill patients may lessen debility.

AMINO ACIDS

Free amino acids are found in both the intracellular and extra-cellular fluid compartments. Skeletal muscle is the largest protein mass in the body. The intracellular concentrations of free amino acids in muscles are approximately

three times greater than those in the plasma. The total intracellular concentration of free amino acids decreases during critical illness. This is due to a large part to the fall in the concentration of glutamine (Askanazi *et al.,* 1980) a nonessential amino acid, which accounts for 60% of the total intracellular pool (Bergstrom *et al.,* 1974). Intracellular concentration of amino acids such as phenylalanine, tyrosine, alanine and the branched chain amino acids leucine, isoleucine and valine usually increases during critical illness (Askanazi *et al.,* 1980). Following convalescence, levels of amino acids return to normal. The concentration of free amino acids in the plasma demonstrates similar alternation to those in the intracellular compartment and hypoaminoacidemia is generally observed in critical illness reflecting the fall primarily in the concentration of non- essential amino acids.

The intracellular amino acid pool is quantitatively the most important but the extracellular compartment is principally involved in amino acid transport between several regional microvascular beds, such as gastrointestinal tract, skeletal muscle, and liver. Therefore, net release or storage of amino acid is often determined from analysis of the extracellular compartment. During critical illness the net release of amino acid from peripheral tissue is increased. A study of burn patient showed that the net release of amino acid nitrogen was five times greater in the patients than in the control subject (Aulick *et al.,* 1979). The rate of amino acid release was related to total burn size (injury severity) and appeared to represent a generalized metabolic response to critical illness. The accelerated peripheral release was matched by increased amino acid uptake across the splanchnic bed (Wilmorre *et al.,* 1980). The amino acids, glutamine and alanine together account for a large portion of the total amino acid nitrogen exchanged between regional tissues (Garber *et al.,* 1976). These appear to be the major nitrogen carriers in the circulation, although all amino

acids are required for protein synthesis. Glutamine and alanine both appear to have specific physiological roles as well. Alanine is a major precursor for hepatic production of glucose. In that conversion the nitrogen is incorporated into urea, which is subsequently excreted by kidneys. Urea is the final step in the breakdown of body protein and usually represents an irreversible loss of nitrogen.

Glutamine is the non-essential amino acid, which has long been recognized to serve as a precursor for the production of ammonia in the kidney. This can be an important buffering mechanism for excreted acid. In addition glutamine has a gluconeogenic potential through its conversion to Krebs cycle intermediates. However, in the last several years other key roles for glutamine have been discovered. It appears to be an important determinant of net skeletal muscle protein breakdown (Johnson *et al.,* 1986). A variety of studies of intact animal ex-vivo preparation, and cell culture all, document a relationship between intracellular glutamine concentration and either the protein synthesis rate or net rate of protein degradation.(Johnson *et al.,* 1986; Smith *et al.,* 1986). Glutamine is an important respiratory fuel for gastrointestinal tract (Souba *et al.,* 1983) and probably other cell types as well, especially those that rapidly proliferate, like bone marrow, fixed immunologic cells and ploriferative cells in the wound and other foci of inflammation.

In short accelerated dissolution of muscle protein during critical illness provides a ready supply of amino acids to support protein synthesis in the wound, the liver and other remote sites. Analine and certain other amino acids may also be utilized for glucose production by the liver and to a lesser extent the kidney. Glutamine appears to be a specific fuel for the gastrointestinal tract where it is converted to alanine. Unfortunately this enhanced mobilization of

amino acids from muscle protein leads to an irretrievable loss of nitrogen in the form of urea, ammonia, creatinine, uric acid and other compounds that are excreted. The net effect on the patient is rapid erosion of muscle mass and worsening debility.

CARBOHYDRATE

Injury and critical illness result in major perturbation in glucose metabolism. Hyperglycemia, glycosuria and impaired glucose tolerance are common findings in critically ill patients and have led to the term 'diabetes of injury'. These signs appears promptly during the ebb phase and persist until convalescence is largely completed. Initially insulin output appears to be decreased, but normal or slightly elevated fasting insulin concentrations are usually found during the hyperdynamic flow phase (Allison *et al* 1968) (Table a). In response to glucose load, insulin concentration may be supranormal (Black *et al.*, 1982).

Table a. Fasting Glucose and Insulin Concentrations

SUBJECTS	GLUCOSE (mg/dl)	INSULIN (U /ml)
Normals (n = 49)	78 ±1	12 ± 1
Trauma patients (n = 19)	104 ± 2*	17 ± 2*

* P < 0.02

During the flow phase of convalescence, hepatic glucose production is stimulated and glucose flow throughout the extracellular fluid compartment is increased. The rate of glucose oxidation may be more than doubled during the flow phase (Gump *et al.*, 1974) Gluconeogenic amino acids released by muscle catabolism at the periphery provide substrate for the increase in hepatic gluconeogenesis. Not only is hepatic glucose output increased, but also the

inhibition by exogenous glucose infusion is blunted (Long *et al.*, 1976). Kinney (1977) has speculated that the increased glucose production is adaptive as it provides a substrate for the synthesis of acute phase glycoprotein and for connective tissue requirements of glucosoaminoglycans and fibroblast.

Glucose also serves as a fuel for many cell types in healing wounds. The oxygen consumption of both injured and uninjured limbs was comparable but glucose uptake by the injured leg was significantly elevated. This was also associated with an increased release of lactate produced by an aerobic glucose oxidation.

The increase in total glucose production and flow appears to correlate with the increase in oxygen consumption (injury severity) in patients with burns or other injuries. However, the respiratory quotient is typically in the range of 0. 7-0. 8, indicating that fat is the principal substrate being oxidized. The increased glucose production by splanchnic tissue is associated with an increased uptake of both lactate and glucogenic amino acids, especially alanine. Thus, the enhanced glucose production seen in critical illness reflects both synthesis of new glucose from amino acid and recycled glucose from lactate. Wolfe *et al.*, (1987) has documented increased glucose cycling in patients with burns. The increased mass flow of glucose while serving as a fuel for healing wounds and inflammatory tissues also reflects inefficient 'futile' cycling that serves mainly to produce heat.

Despite of an increased mass flow of glucose during critical illness, patients are usually intolerant to exogenous glucose administration. Black and co-worker (1982) induced and maintained fixed hyperglycemia in both patients recovering satisfactorily from multiple trauma and age-matched controls. In the control subjects, glucose disposal continually increased in association with

steady rise in serum insulin concentrations. However, in patient recovering from trauma, glucose disposal in response to fixed hyperglycemia was relatively steady despite insulin concentration were consistently greater than those achieved in the normal. In injured subjects no association between glucose disposal and insulin concentration was found. Glucose disposal was generally in the range of 6 to 7 mg/kg-min even though the insulin concentrations were high.

In other studies, insulin was infused to maintain fixed hyperinsulinemia, and sufficient glucose was administrated to maintain, euglycemia. Glucose disposal was lower in patients than in controls at all doses and concentrations of insulin achieved. These studies provided quantitative evidence of insulin resistance in patients recovering from injury. This apparent limitation in the ability to utilize to glucose during critical illness has been demonstrated in other studies as well (Wolfe *et al.*, 1979,1980). This limitation seems to be related to the severity of injury (Table b). Therefore in the ICU the most seriously ill patients are progressively less able to utilize glucose to meet their total energy requirements.

Table b. Limits of Glucose Oxidation or Disposal

Severity Of Illness	Disposal Rates			
	Mg/kg. .min	G/kgday	Kcal/day (70kg)	Study
Postoperative	7	10.1	2400	Wolfe
Moderate injury	6	8.6	2050	Black
Severe burn	5	7.2	1710	Wolfe

LIPID

Fat oxidation tends to maximize between 8-14 days after injury. In contrast to stores of protein (6-7kg) and carbohydrate (a few hundred gms) fat stores are large, normally accounting for about 14kg. of the body weight in a healthy 70kg man (Table c).

Table C. Average Adult Body Composition

COMPONENT	%BODY WEIGHT	Kg	CALORIC VALUE
Carbohydrates (glucose, glycogen)	1	<1	1,000
Fat (adipose, triglyceride)	20(variable)	1.4	1,30,200
Protein (muscle, plasma proteins)*	20	14	56,000
Water	55	38.5	0
Minerals	3-5	2-3.5	0
Total	100	70	

* Approximately one half of body protein is relatively metabolically inert and exists as structural protein in connective tissue, skin, cartilage, and bone. The remainder (6 - 7 kg) consists of visceral, plasma, and skeletal muscle protein, which is in a dynamic state.. These proteins, which exist in the hydrated state,constitute the body cell mass. The readily available body caloric reserve of protein is therefore about 28,000 calories.

Fat reserves are mobilized by lipolysis of triglycerides to glycerol and free fatty acids. The fatty acids are used both in liver and peripheral tissues as a source of energy. The increased lipolysis following injury is presumably regulated by the amount of 3'-5' cyclic adenosine monophosphate, which in turn regulates the enzyme triglyceride lipase (Carlson, 1970). In post-injury state, patients continue to burn fat even when given large amount of glucose. The failure of

exogenous glucose to limit fat oxidation is characteristic of hypermetabolic critically ill or injured patients.

The triacylglycerol in adipose tissue is the primary lipid fuel reserve. After hepatic synthesis, triacylglycerol is incorporated into very low-density lipoproteins and transported in blood. In the peripheral tissue, hydrolysis precedes tissue uptake of fatty acids, which constitutes a major fuel source for all tissue except red blood cell and brain. Free fatty acids are normally the major source of energy for resting skeletal muscle.

Plasma free fatty acids are elevated after injury; elevations are greatest with sever injury. Normally the free fatty acids content of plasma and the metabolic turnover of fatty acids are directly related. The rate of lipolysis is typically sensitive to circulating levels of catecholamines, although glucagon and adrenocorticotropic hormones also modulate the response under some condition (Brike *et al.,* 1972). Insulin stimulates both glucose and free fatty acid uptake in adipose tissue. In short the balance between fat mobilization and storage is the result of complex neurohormonal interactions to which in the setting of injury and acute illness, must be added the effects of major pertubation in blood flow to the adipose tissue, muscle and liver which depend on the post-injury interval and other uncontrollable variables.

Glaster *et al.,* (1984) used stable isotope measurement techniques to quantitative plasma palmitate turnover in patients with uncomplicated thermal burns of moderate severity. Although there was considerable variability, fatty acid flux and plasma fatty acid concentration in burn patient were directly related as they were in healthy. They also found that palmitate flux was directly related to severity of injury. Fatty acid turnover measurements reflect the net lipolytic rate, since fatty acids liberated from adipose tissue by the hydrolysis

can be re-esterified locally. Glycerol, however, cannot be re-esterified and plasma glycerol turnover represents the absolute lipolytic rate.

Glycerol turnover was measured in injured and infected patients by Carpentier *et al.*, (1979), and was found to be about twice normal, in contrast to the more modest 20-30% increase observed by Galster (1984). Several methodological differences may explain this disparity. In Carpentier's study plasma glycerol was elevated whereas in Galster's study it was decreased.

Studies in burns patient (Wolfe *et al.,* 1987) indicated that increased rate of fatty acid turnover is due in part to increased cycling of fatty acids and glycerol, that is the hydrolysis of triglycerides and re-esterification of fatty acids with glycerol, a cyclic process resulting in no net quantitative change of substrate. The purpose of this and other futile cycles is not clear, but since they usually involve the net generation of heat they may contribute to the increased heat production or hypermetabolism of critical illness.

REGULATION OF THE METABOLIC RESPONSE IN CRITICAL ILLNESS.

It has been useful to consider the regulatory mechanism of the response to critical illness as a component of neurohormonal reflex arc (Wilmore *et al.*, 1976). Afferent signals alert the body to the presence of an injury, invading bacteria, hypoxia, acidosis and even to the presence of potential danger. Afferent input also indicates the presence, extent and resolution of the inflammatory tissue or wound. The brain and central nervous system, and perhaps other organ systems presumably process and interpret the afferent input and generate efferent signals that controls the regional and systemic metabolic alteration observed clinically.

ENDOCRINE MEDIATORS

One of the most familiar neurohormonal reflex arcs is the endocrine system. During critical illness the concentrations of catabolic counter regulatory hormones-cortisol, glucagon and the catecholamines, epinephrine and nor-epinephrine are typically increased. These hormones serve as effector signals in the response to critical illness. Increase in concentration correlates with the severity of illness (Wilmore *et al.,* 1974; Vaughan *et al.,* 1982; Davies *et al.,* 1984). The catecholamines appears to play a role in development of hypermetabolism (Harrison *et al.,* 1967; Wilmore *et al.,* 1974). Catecholamine turnover is proportional to burn size and hypermetabolism may be significantly decreased by α and β blockade. The catecholamines also influence normal glucose and insulin relationship Porte *et al.,(*1973), demonstrated the influence of sympathoadrenal axis on insulin response to glucose. Insulin concentrations were substantially reduced with α-stimulation but they were enhanced by β-agonists. The catecholamines may also affect peripheral insulin action. The metabolic effect of cortisol include muscle wasting, glucose intolerance and sodium retention. Glucagon stimulates hepatic glucose production.

Shamoon *et al.,* (1981), observed a synergistic effect of three counter-regulatory hormones; cortisol, glucagon and epinephrine-on glucose production in humans suggesting that combined hormonal effects were more complex than the addition of individual hormone action. Bassey *et al.,* (1984), infused a mixture of hydrocortisone, glucagon and epinephrine into normal person for 3 days. This hormonal infusion achieved concentrations of counteregulatory hormone similar to those observed in patients with mild to moderate injury. In addition, it resulted in increased resting heart and respiratory rates, widened pulse pressure and slightly elevated rectal temperature when compared with

those of the same subjects during a control saline infusion. Hypermetabolism, negative potassium balance, increased endogenous glucose production, insulin resistance, sodium retention and leukocytosis were also observed.

During studies with control subjects who were maintained in nitrogen equilibrium by consuming a standard constant diet, when subjects were given hormonal infusion the subjects were in persistently negative nitrogen balance even though the nutritional intake was identical to control. Whole body protein turnover was increased with hormonal infusion and this was due largely to increase in protein catabolism. Thus, simple alteration of the hormone environment, stimulated many of the metabolic responses to injury even in the absence of a wound or inflammatory focus. The hormonal interactions were complex. For example, the increased metabolic rate appeared to represent additive effects of the hormones whereas the negative nitrogen balance demonstrated synergistic interaction.

The development of insulin resistance appeared to be due entirely to the action of cortisol. Additional studies demonstrated a fall in skeletal muscle intracellular amino acid concentration following triple hormonal infusion (Bessey *et al.,* 1989). This was due largely to a decrease in intracellular glutamine. In view of the potential regulatory role of glutamine in muscle, these observations suggested that the hormonal environment might play a causative role in increasing net skeletal muscle proteolysis. However, other findings did not support that conclusion. Triple hormone infusion did not alter whole blood amino acid concentration or amino acid efflux from forearm. Although hormonal blockade has resulted in reduction of net skeletal muscle proteolysis following injury (Hulton *et al.,*1985), alternation of the hormonal environment alone was not a sufficient stimulus to accelerate net skeletal muscle proteolysis. Thus, the

stress hormones appear to be necessary but not completely responsible for the proteolytic response to critical illness. Other factors, therefore, must be involved in the determination of these clinical phenomena.

PEPTIDE REGULATORY FACTORS (Cytokines)

In the last several years, investigators have identified an ever-increasing number of substances elaborated by inflammatory cells that influence the recruitment, ploriferation or function of other cell (Table d).

As a group, these substances are known as peptide regulatory factors or cytokines. Some of these factors have primarily immunomodulatory effects and others affect cellular proliferation, growth and differentiation. Some of the factors influence neighboring cells (paracrine action), some affect the cell from which they were secreted (autocrine action) and a few of these substances also appear to be able to affect cells in the remote sites and thus exert systemic (endocrine) effects. These latter may contribute to the metabolic responses to critical illness.

INTERLUKIN-1 (IL-1)

Interlukin-1 is now recognized to be a protein or a family of proteins, which appears to play a major role in acute phase response to infection. IL-1, immuno-reactivity has been demonstrated in the hypothalamus of human (Breder *et al.,* 1988), indicating that IL-1 may be an intrinsic neuromodulator in the central nervous system pathways that mediate the acute phase response. Baracos *et al.,* (1983) reported increased muscle proteolysis in vitro when tissue were incubated with monocyte supernatant of IL-1. They further

proposed that IL-1 induced elevated concentration of prostaglandin E_2, which was responsible for the increased proteolysis.

Other studies in intact animal suggested that IL-1 or one of its breakdown products could produce hypermetabolism, increased amino acid oxidation, and increase myofibrillar protein breakdown (Clowes *et al.*, 1983). Watters *et al.*, (1985) stimulated the production of IL-1 in the normal human with daily injections of steroid compound eticholanolone, which resulted in sterile inflammation. Although the subjects manifested an acute phase response, they were not hypermetabolic and they remained in the nitrogen equilibrium on a standard diet. The concentrations of catabolic hormones were not affected by the eticholanolone injections. However, when these were administered to subjects receiving an infusion of catabolic hormones, both inflammatory and metabolic responses were observed (Watters et al., 1985). This suggests that both specific inflammatory and metabolic mediators together determine the clinical response to critical illness.

TUMOR NECROSIS FACTOR (TNF)

TNF is elaborated by activated macrophages and other inflammatory cell types (Old, 1985). The physiologic effects of TNF are dose related. Low concentration can reflect wound remolding and other inflammatory cell functions, whereas, high dose can produce shock and death. Michie *et al.*, (1988) administered recombinant human TNF to patients observed a dose dependent rise in the TNF concentration and to symptoms of headache, myalgia and chills, fever, tachycardia and increase in ACTH indicating activation of the adrenal pituitary axis. These all developed 30-60 minutes after infusion. When these observation

were compared with those of normal subjects who received endotoxin were similar to those following TNF

The importance of TNF in mediating the response to endotoxin was dramatically demonstrated in studies (Tracey *et al.,* 1987) when lethal doses of endotoxin were administered to baboons, death could be completely prevented by prior administration of TNF antibody. In human when the cyclo-oxygenase inhibitor ibuprofen was given prior to endotoxin, the sustemic symptoms and endocrine responses were attenuated even though the rise in TNF concentrations and subsequent leucocytosis were still present (Revhaug *et al.,* 1988). Thus TNF seems to be an important mediator in response to endotoxin, and it appears also to activate cyclooxygenase pathways.

INTERLUKIN-2 (IL-2)

Interlukin-2 also is associated with toxic effects, including fever, tachycardia, flu-like symptoms and elevations of the counteregulatory hormones. These responses are similar to those observed after endotoxin (Michie 1988).

INTERLUKIN-6 (IL-6)

Interlukin-6 is elaborated by inflammatory cells, can stimulate myeloid cell growth as well as T-cell proliferation and differentiation often in association with IL-2. IL-6 also appears to have a dominant effect on the hepatocyte synthesis of acute phase proteins (Feurer *et al.,* 1986). IL-1, and TNF appears to be accessory signals. Given the central importance to critical illness IL-6 may prove to be an important systemic mediator as well.

Table d. Peptide Regulatory Factors-Cytokines

FAMILY	SOURCES	TARGET CELLS
Interleukins(IL 1-11)	Monocytes/macrophages, Fibroblasts,epithelial Cells	Hematopoietic cells, fibroblasts, lymphocytes, hepatocytes, brain
Tumor necrosis factors (TNF α,β)	Monocytes/macrophages, Lymphocytes	Endothelial cells; monocytes/ macrophages neutrophils, fibroblasts; liver, muscle, lung, gut, kidney
Interferons (IFN αβϒ)	Monocytes/macrophages, Fibroblasts, epithelial Cells	Multiple immune cells,phagocytes
Colony stimulating factors (Granuloeyte CSF, Macrophage CSF, GM-CSF, erythropoietin)	Granulocytes, Macrophages Juxtaglomerular cells	Granulocyte precursors, erythroid precursors, monocytes/ macrophages
Growth factors (Epidermal GF; fibroblast GF; insulin-like GF 1,2; nerve GF; platelet-derived GF; transforming GF αβ)	Multiple cell types	Multiple cells

NUTRITIONAL ASSESSMENT IN CRITICALLY ILL PATIENTS

In patients with multiple injury, shock, sepsis, major surgery, burns etc. a state of hypermetabolism develops which leads to extensive mobilization of carbohydrate, protein and lipids, which has been alreadily described previously. Increased protein catabolism can lead rapidly to sever wasting of the lean body mass, impairment of vital organ functions and diminution in critical reparative and immune processes even in previously healthy person. This situation demands increase in caloric requirements of the patient over and above the basal needs. In-spite of trying hard to fulfill the increased requirement of the nutrients by enteral or parenteral dietary formulae, a state of malnutrition is not corrected fully. Hence repeated assessment of nutritional status gives the idea about the state of metabolism in critical illness. Thus the serial measurement of parameters that indicate nutritional status helps in planning the dietary formula. The complexity and heterogeneity of the diet, and the multiple effects that the nutrients have on tissue and organ structure and function make it inevitable that there can be no definitive test of nutritional status. In particular for the assessment of protein energy status (only one part of the overall nutritional status), no single test or technique has been found to be both sensitive and specific indicators of malnutrition. Indeed many of the test are affected by non-nutritional aspects of the response to illness.

A number of assessment strategies therefore have been developed and various combinations of these may be employed.

A. SUBJECTIVE GLOBAL ASSEMENT (SGA)

The SGA incorporates the following information from the patients' history.

- Weight change; the amount and rate of weight loss and its pattern during the previous six months.
- Dietary intake in relation to the patients usual pattern.
- Significant gastrointestinal symptoms.
- Overall functional capacity or energy level.
- Metabolic demands of the patient underlying disease state.
- Physical examination . which includes.

1. Measurement of skin folds in the triceps region to determine the loss of subcutaneous fat.

2. Palpation of muscle bulk of deltiod muscle which indicates the state of protein catabolism

3. Presence of edema (abnormal collection of fluid in tissues) which may be the results of hypoprotenemia due to increased protein catabolism.

SGA is carried out with the fore mentioned clinical data noted either normal, mild, moderate or sever. A major limitation of SGA is lack of quantitation and therefore limited sensitivity in assessing change in the nutritional status following therapy. To quote Lord Klevin (William Thomas, former Professor of physics at Glasgow University) "--- when you can measure what you are speaking about, and express it in numbers, you know something about it --- when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts, advanced to the stage of science ---".

B. ANTHROPOMETERY

Anthropometric measurements are used to estimate subcutaneous fat which constitutes approximately 50% of the body fat stores and skeletal muscle bulk,

which represents 60% of the total body protein pool and the major sources of amino acids during stress and starvation. The measured values are compared with data from standard controls, which tends to produce a wide range of normal values.

a. Skinfold Thickness : This is used to estimate total body fat in the region of triceps, biceps, supra iliac regions. Regression equation relating skin fold thickness to the body density can be used for conversion of the skin fold measurement to body fat content (Durnin and Womerrsly, 1974). The measurements of skin folds using calipers is inexpensive, simple, non-invasive and can be performed at the bed side. There are some practical problem however. The site of skin fold measurement may be inaccessible because of burns or bandages. The extent of the skin compressibility may vary especially in edematous and obese patients. Another major limitation of skin fold measurement is that subcutaneous fat is not a constant proportion of the total body fat estimates of the percentage of the total body fat represented by the subcutaneous fat ranges from 20-70% depending on the factors such as age, gender, obesity and even measuring technique.

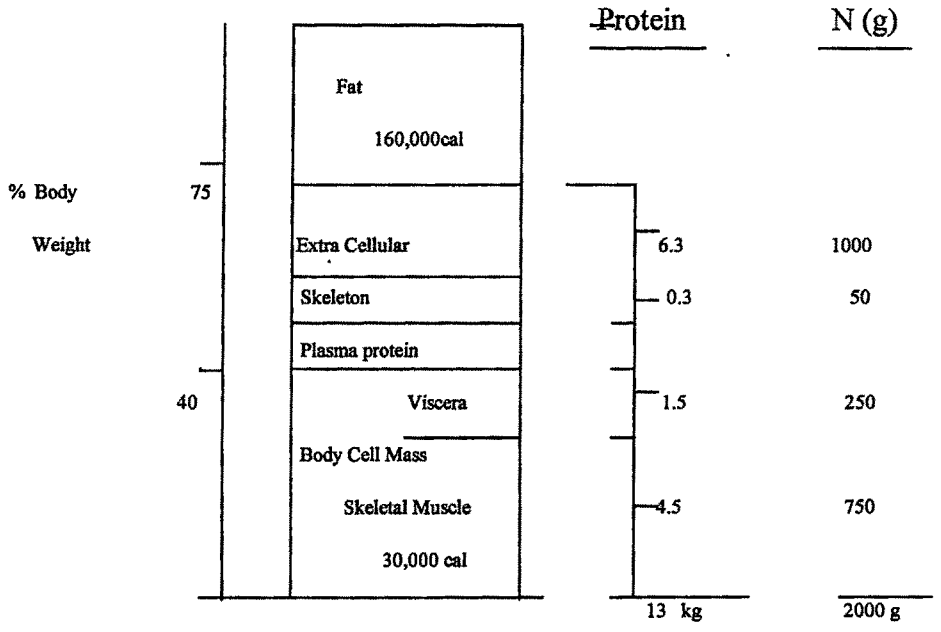
b. Arm Circumference : Arm circumference in association with tricep skin fold thickness has been used to estimate midarm muscle circumference as an indicator of protein energy malnutrition (Bistrian *et al.*, 1975). The value of anthropometric measurements in assessing seriously ill patients is limited.

C. BIOCHEMICAL TEST

1. PLASMA PROTEINS

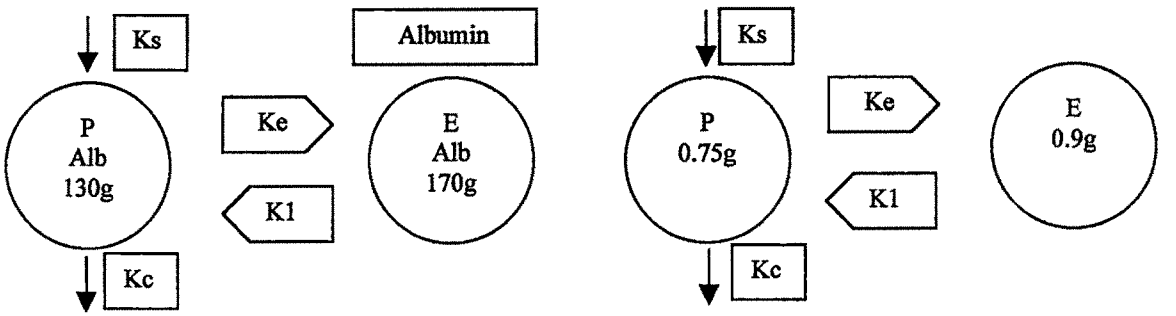
The plasma proteins albumin, transferrin, and prealbumin have been described as nutritional indicators because they have been thought to reflect the

availability of amino acids for hepatic protein synthesis (Buzby *et al.*, 1980). These proteins are synthesized by liver and secreted into the plasma. Albumin is the most abundant of these proteins, and the human serum contains 35-40gms/l. In the hepatocyte, it is not native albumin that is formed but a series of precursors, the first of which is known as pre-pro-albumin which differs from native albumin by 24 additional amino acid residues. It takes 25-30 mins for an albumin molecule to be synthesized by the polysomes and secreted into the plasma. Albumin is not stored in hepatocytes but is continuously secreted into the plasma at an estimated rate of 17 g/day and turned over with a half-life of approximately 21 days. In critically ill patients negative nitrogen balance occuring as a part of hypermetabolism, is reflected in various protein compartments.[Figure 1]



The figure. 1, show relative size and protein content of four major body compartments. Body cell mass is cellular and metabolically active compartment.Visceral and plasma proteins are in rapid turnover and need to be actively replaced if the functional capacity of the internal organs is to be maintained the protein pools of the visceral tissue are small and the most vulnerable during periods of metabolic stress and starvation. Their are approximately 100 gms of labile expendable protein nitrogen in the storage (Shikora and Blackburn, 1991)

Since albumin, transferrin and prealbumin are the most readily available proteins that fulfill the amino acid requirement for the increased protein synthesis and gluconeogenesis in the liver, they are frequently decreased in the critical illness. The daily exchange of albumin between the extravascular and intravascular space, however, is 10 times the albumin synthesis rate because acute disease increases the transcapillary escape proteins, it has a much more profound effect on the concentration of these proteins in the plasma (Fleck 1988) [.Figure 2].



The relationship of albumin and prealbumin exchange, between blood and tissue to their synthesis and catabolism.

K1=fractional loss of protein to intravascular pool

Ke=fractional loss of protein to extravascular pool

E=extravascular pool

P=intravascular pool

Ks=rate of synthesis

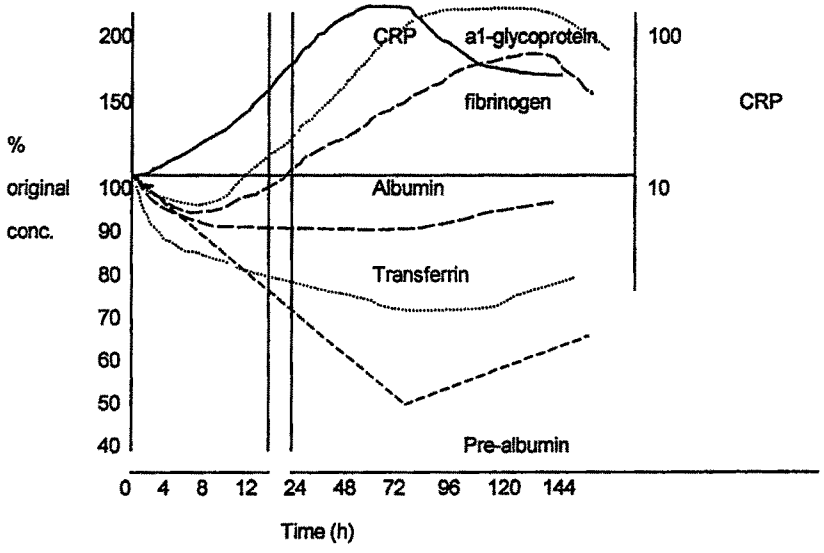
Kc=rate of catabolism

.An another factor that is responsible for hypoproteinemia is unavailability of the amino acid substrates for the synthesis of albumin, transferrin and prealbumin in the liver because of the malnutrition. As the provision of the adequate nutrition is difficult in critical illness they are frequently malnourished. Despite the apparent adequacy of the nutritional support, nitrogen balance is frequently negative, especially while the patient is in the intensive care unit.

Thus in critical illness serum albumin, transferrin and prealbumin are decreased due to following reasons;

1. Increased catabolism of these proteins
2. Decreased synthesis of these protein due to unavailability of substrates
3. Escape of these proteins into the extra-vascular space

On one hand these proteins are decreased in serum and on the other hand proteins like fibrinogen, c-reactive protein and haptoglobin are increased in the plasma. The latter ones are designated as acute phase reactants [Figure 3]



Response of plasma proteins after injury (Fleck, 1988)

Although a high priority is given to synthesis of acute phase proteins, the magnitude of the acute phase response to surgery (and perhaps to severe infection) is affected by nutritional status (Cruickshank *et al.,* 1989).

In critically ill patients, therefore, plasma concentrations of albumin, transferrin and pre-albumin tend to be lowered and return to normal as the disease process itself recovers. Shenkin *et al.,* (1980), studied a number of biochemical indices of nutritional status in patients during the eight day period following severe trauma. During this immediate post-trauma period, plasma levels of albumin, transferrin, prealbumin and retinal-binding protein did not reflect the improvement in nitrogen balance achieved in patients who received parenteral nutrition with high nitrogen content.

The actual rate of recovery from hypoproteinemia may be impaired by malnutrition, however, and the delay in recovery of plasma protein levels in malnourished patients may be reduced by providing nutritional supports. As a result,although measurements of these plasma proteins like albumin, transferrin and pre-albumin may be of little value in the initial nutritional assessment of the critically ill, serial measurements of these proteins could be useful in monitoring the response of patients to nutritional support.

a) Albumin

Plasma albumin concentration is a valuable test for predicting outcome (Reinhaardt *et al.,* 1980) but its long half life 21 days and its insensitivity to pure nutritional depletion (Starker *et al.,* 1982) make it a poor nutritional marker. The need for albumin infusion some patients further invalidates plasma albumin concentrations in nutritional assessment.

b) Transferrin

Plasma transferrin has a shorter half-life of 8-days, and is more sensitive to change in nutritional state (Ingelbleek and Van de Scchriek 1975). It may be useful as a nutritional marker in population studies but it lacks the sensitivity and specificity required for use in individual patients (Church and Hilll, 1987). Church and Hill have stated that a rising level is a reasonably good indicator of a positive nitrogen balance, but a falling level was a poor indicator of the reverse. It is also important that iron deficiency induces increased synthesis of transferrin, which may complicate interpretation of serum transferrin results.

c) Pre-albumin

Pre-albumin with its short half-life of 2 days, has been shown in a number of studies to be a sensitive index of visceral protein status and a useful marker of response to nutritional support (Douville *et al.,* 1982) Changes occur within 7 days of change in nutrient intake (Selzer *et al.,* 1982). In Church and Hill's (1987) study of general surgical patients, 93% of patients with rising plasma pre-albumin levels had a positive nitrogen balance.

2. NITROGEN BALANCE / URINE NITROGEN

The most common clinical method for assessing protien turnover is determination of nitrogen balance which is a measure of the daily intake of nitrogen minus excretion. The intake represents nutritional nitrogen and the excretion consists of measured urinary nitrogen plus a factor for unmeasured gastrointestinal and cutaneous losses - usually 2- 4g. In acute catabolism, tissue protein breakdown leads to increased loss of nitrogen into urine, which, together with obligatory losses, results in negative nitrogen balance (Shaw *et al.,* 1987). Measurement of total urine nitrogen is technically difficult and time

consuming using the classical Kjeldahl method (Fleck and Munro 1965), although results can be achieved readily using a chemiluminescence analyzer (Grimble *et al.,* 1988). This apparatus is relatively expensive and therefore is not widely used. So, because, approximately 80% of the total urine nitrogen usually is in the form of urea, an easily measured substance, urine nitrogen usually is estimated from the urine urea concentration. There are marked intra and inter-individual variations in the proportion of urine nitrogen excreted as urea. For example, Burgess and Fleck (1990), found that urea nitrogen varied between 58% & 100% of total urine nitrogen over the course of 1 week of treatment with total parenteral nutrition.

Because urea is evenly distributed in the body water, changes in body water content may cause changes in serum urea concentration and may cause errors in the estimation of nitrogen losses. Moreover, urine nitrogen estimated from urine urea samples infected with urease containing bacteria yields falsely low results. For these various reasons there is a growing support for measuring total nitrogen in urine (Grimble *et al.*, 1988; Konstantinides *et al.,* 1991). If urine nitrogen is measured directly, the collection of 24 hour urine samples remains a notorious source of error even in patients with a urinary catheter and interruption of collections by medical procedures commonly contribute to inaccuracy.

Improvement in nitrogen balance is the single nutritional parameters most consistently associated with improved outcomes, and the primary goal of nutritional support should be the attainment of nitrogen balance. When nitrogen balance cannot be attained in severely catabolic patients, minimization of the nitrogen deficit may be the best that can be achieved (Shaw *et al.,* 1987).

3. CREATININE - HEIGHT INDEX : (CHI)

The amount of the creatinine excreted in urine is an indicator of muscle mass and the total body nitrogen (Forbes 1987; Jeejeebhoy and Meguid 1986). The creatinine height index (CHI) proposed by Bistrain et al.,(1974), is a ratio of a subject's 24 hour urine creatinine excretion versus that of age and height matched controls of the same gender expressed as a percentage. An index of 100% is taken to indicate normal muscle mass provided there is normal excretion of creatinine. Creatinine excretion declines with age and is increased by acute infection, injury and diets high in protein and creatinine. Other potential problems with CHI include the significant inter-individual variations in creatinine excretion and its obvious invalidity in the presence of renal failure. Moreover, intra-individual variation of creatinine excreation may vary as much as 20% from day to day (Forbes 1987), so serial measurements are necessary to achieve an accurate mean excretion.

In the large study of seriously ill patients (Harvey *et al.,* 1981), abnormal CHI was associated with increased sepsis and mortality. Other studies, however, have found the CHI to have little predictive power of adverse clinical outcome (Jeejeebhoy and Meeguidd 1986 ;Jequier 1987).

4. ASSESSMENT OF ELECTROLYTE STATUS

Nutritional assessment with regard to the total body status of major electrolytes usually relies on plasma electrolyte measurement. Urine electrolyte concentrations also may be helpful in some instances. Frequent monitoring of plasma electrolytes is necessary in the critically ill because the balance and distribution of fluid and electrolytes may alter rapidly and profoundly.

The major intracellular electrolytes, potassium, magnesium and phosphorous are required for protein synthesis and the attainment of nitrogen balance (Rudman *et al.*, 1975). Serum concentrations of these electrolytes should be monitored carefully during the institution of nutritional support because serum concentrations may fall precipitously once adequate protein and calories have been provided. This is particularly true in the case of phosphate. These intracellular electrolytes should be provided in amounts sufficient to maintain serum levels within the reference range.

Magnesium

Magnesium deficiency is particularly common in undernourished alcoholic patients and following gastrointestinal loss of magnesium in those with sever diarrhoea, high-output ileostomies. Magnesium is a cofactor for a large number of enzymes, including Na^+ - K^+ - adenosine triphosphatase, which maintains low intracellular sodium and high intracellular potassium concentrations. When hypokalemia resistant to potassium supplements occurs, plasma magnesium is measured to detect magnesium deficiency. In this situation, intravenous magnesium replacement is required in addition to potassium to correct the hypokalemia.

Chronic severe hypomagnesemia impairs parathyroid hormone (PTH) secretion (Pocotte *et al.*, 1991) and may lead to hypocalcemia resistant to treatment with calcium. The clinical signs and symptoms of magnesium deficiency are identical to those of calcium deficiency and include muscle cramps, tetany, and hyperactive tendon reflexes. The diagnosis may be missed if the clinician is not aware that neuromuscular symptoms occuring in the patients with high intestinal losses are more likely to be caused by magnesium deficiency than calcium deficiency. Intravenous magnesium replacement

corrects the hypomagnesemia and hypocalcemia. Adequacy of repletion of magnesium can be monitored by the increase urine magnesium excretion to normal levels (Fink, 1969).

Hypermagnesemia on the other hand is well tolerated and dose not appears to cause clinical symptoms or signs, even when quite marked. The renal failure by far is the most common cause of hypermagnesemia.

Calcium

Hypocalcemia may develop acutely in severe pancreatitis, acute renal failure, severe trauma or over-whelming sepsis and following neck surgery-eg. thyroid or parathyroidectomy. Intravenous calcium is required for acute symptomatic hypocalcemia. The hypocalcemia associated with chronic renal failure and other chronic conditions such as hypoparathyroidism is treated with oral calcium and vitamin D suppliments.

Hypercalcemia in hospitalised patients most frequently is caused by tumors associated with PTH -related peptide production or local release of calcium with bony metastases. Other common causes are hyperparathyroidism and the adminstration of potent vitamin D analogues to renal failure patients. Hypercalcemia associated with immobilization is recognized increasingly in critically ill patients, particularly those who develop renal and respiratory failure and who require prolonged ventilation. It is associated with a profound hypercalciuria, reflecting calcium release from bone. PTH is suppressed. The hypercalcemia may respond to intravenous bisphosphonate administration, but improved mobility is the only definitive cure.

Phosphate

Hypophosphatemia is relatively common in hospitalized patients (Knochel., 1977). Intravenous administration of glucose stimulates insulin secretion, which

increases the transport of glucose and phosphate into the cell which may result in rapid lowering of the plasma phosphate concentration. Re-feeding after a period of starvation also promotes anabolism and intracellular shift of phosphate resulting in hypophosphatemia. This also may occur in any condition causing a respiratory alkalosis. Hypophosphatemia also may be caused by losses from the gastrointestinal tract or by decreased absorption of phosphate in mal-absorptive states. Intravenous glucose administration may precipitate profound hypophosphatemia in malnourished alcoholic patients with chronic phosphate depletion. The clinical manifestations of phosphate depletion depend on the duration of the hypophosphatemia and on the absolute decrease in the plasma phosphate concentration. In general, the lower the plasma phosphate level and the longer the deficiency, the greater the clinical consequences.

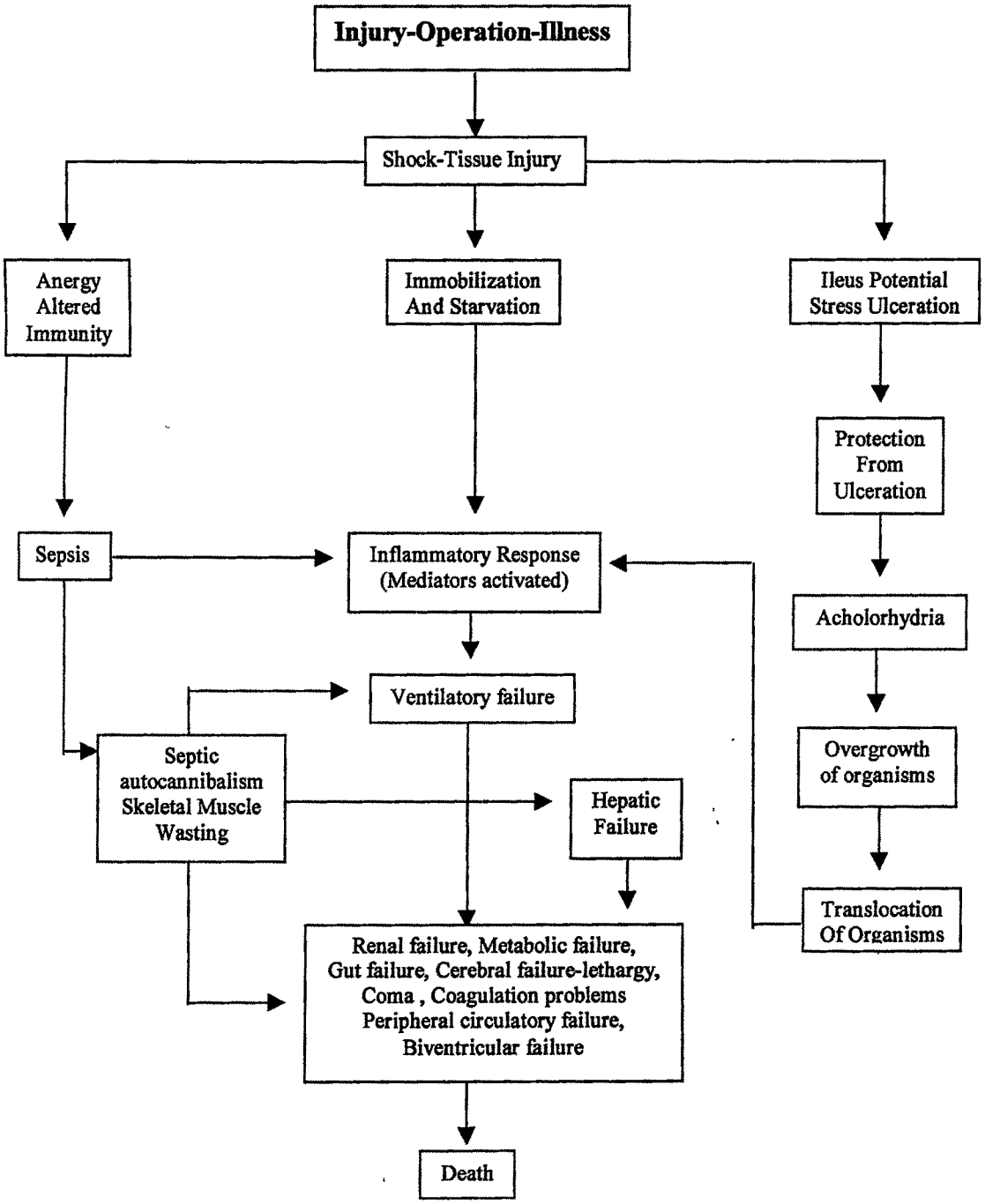
MULTIPLE ORGAN SYSTEM FAILURE (MOSF)

Multiple organ system failure (MOSF) is a general intensive care unit syndrome and one of medical progress because it has appeared or developed only because of our technologic and clinical capabilities in supporting patients with organ dysfunction (Arthur, 1991). The syndrome of multiple organ failure is the final common pathway for number of clinical problems, including sever multiple system trauma, an operation with or without complication, infection such as peritonitis, and sever illness with limitations in organ function or cardiac output secondary to aging, arteriosclerosis, or chronic diseases (Baue, 1990).

MSOF is said to manifest when more than one or two systems or organs cannot support their various activities spontaneously; (Knaus *et al.*,1985, Baue, 1990). No matter what the cause of MOF, there is a high mortality rate

that depends on the number of organs or systems that have failed, with three or more organs failed the mortality rate approaches 60-80% [Figure 4]

(Arthur,1991) Factors that contribute to MOF and death after injury



There are number of common threads that can be observed in development of MSOF. First of all, frequently there is a shock, ischemia, or circulatory instability after injury or illness, cardiac output must increase (Albrecht M., Clowes GHA.1964).Secondly, immobility because of injury, operation, shallow breathing, and dependency produces mechanical problems (Border *et al.*, 1976). Third, tissue injury and inflammation causes overwhelming activation of cellular humoral mediators. Fourth, infection produce systemic activation of all of these responses, the interleukins, cachectin (tumor necrosis factor),and other factors. Fifth, gut failure septic syndrome: diffuse atrophy of bowel mucosa with bacterial overgrowth, translocation of organisms across the mucosa into mesentric lymph nodes, and inflammatory mediators stimulation. Finally, metabolic demands on the skeletal muscle and the liver results in protein metabolic failure-septic auto-cannibalism and hepatic failure of sepsis (Cerra *et al.*, 1980).

For sometime, sepsis has been used as a noun to refer to an infectious process produced by bacteria, viruses, fungi or other organisms. More recently, the word has been extended to include patients with a clinical picture of sepsis, which may be secondary to sever inflammatory processes, or with tissue injury and necrosis but without bacteriologic evidences of infection during life or at autopsy. Inflammatory agents can produce such a problem in experimental animals (Goris *et al.*,1985)

In short the basic fact working behind the development of MSOF is, a failure of host defence homeostasis in which the products of this defense are injurious to the host as well as to the invading organism (Goris *et al.*,1985)..

Despite high morbidity and mortality, it is encouraging that some patients recover even an advanced stages of MSOF. This suggests that the syndrome

is, to some extent, reversible. Thus studying the concept of MSOF helps us to decide the management stratergy of such patients so as to support organ function prospectively and prevent failure. So it is with nutritional support. The susceptible sick patient should receive adequate nutrition by the best means available to prevent gastrointestinal problems, to support the liver, to maintain the musculo-skeletal function for breathing, coughing, and ambulation; and to provide the material needed to repair and healing of the wounds and area of injury.

ARTERIAL BLOOD GAS ANALYSIS

PHYSIOLOGIC FEATURES

The primary functions of respiratory system are to remove the appropriate amount of carbon dioxide from blood entering the pulmonary circulation and to provide adequate oxygen to the blood leaving pulmonary circulation. In order for these functions to be carried out properly, there must be (1)adequate provision of fresh air to alveoli for delivery of oxygen and removal of carbon dioxide (ventilation), (2) Adequate circulation of blood through pulmonary vasculature (perfusion), (3) Adequate movements of gas between alveoli and pulmnory capillaries (diffusion) and (4) Approprite contact between alveolar gas and pulmonary capillary blood (ventilation-perfusion matching).

GAS EXCHANGE

The partial pressure of carbon dioxide ($PaCO_2$) in arterial blood is directly proportional to the amount of CO_2 produced per minute (VCO_2) and inversly proportional to alveolar ventilation (VA). At a fixed VCO_2 when alveolar ventilation increases $PaCO_2$ falls; and when alveolar ventilation decreases

$PaCO_2$ rises. Maintaining a normal level of O_2 in alveoli (and consequently in arterial blood) also depends upon provision of adequate alveolar ventilation via breathing.

Both CO_2 and O_2 diffuse readily down their respective concentration gradients through the alveolar wall and pulmonary capillary endothelium. Under the normal circumstances this process is so rapid that the equilibrium of both gases is completed within one-third of the transit time of erythrocytes through pulmonary capillary bed.

In ideal situation, all alveolar-capillary units have equal matching of ventilation and perfusion. But even in normal individuals some ventilation perfusion mismatching is present as there is normally a gradient of blood flow from the apices to base of the lungs. Moreover, there is a similar gradient of ventilation from the bases to apices. Therefore, the blood coming from the apices has a higher PO_2 and lower PCO_2 than blood coming from the base. The net PO_2 and PCO_2 of resulting mixture of blood coming from all areas of the lungs is a weighted average of the individual components, which takes into account the relative amount of blood from each unit and the O_2 and CO_2 content (saturation) of blood coming from each unit. Thus it becomes important to distinguish between the partial pressure and the content of O_2 in blood. Hemoglobin is fully saturated at PO_2=60 mmHg and little additional O_2 is carried by hemoglobin even with substantial elevations of PO_2above 60 mmHg. On the other hand, significant O_2 de-saturation of hemoglobin occurs once PO_2 falls below 60 mmHg on to the steep descending limb of the curve.

MEASUREMENT OF GAS EXCHANGE

The most commonly used measures of gas exchange are the partial pressures of O_2 and CO_2 in the arterial blood i.e. PaO_2 and $PaCO_2$, respectively. These partial pressures do not measure directly the quantity of O_2 and CO_2 in blood, rather the driving pressure for the gas to be carried in blood. Most commonly, PO_2 is the measurement used to quantitate the adequacy of oxygenation of arterial blood. The adequacy of CO_2 elimination is measured by the partial pressure of CO_2 in the arterial blood i.e. PCO_2.

MECHANISMS OF ABNORMAL FUNCTION

A] **Hypoxia** is a common manifestation of variety of disease affecting lungs or other parts of the respiratory system. The four basic mechanisms of Hypoxemia are

1) Decreased oxygen in inspired air as occurs at high altitude

2) Hypoventilation; as occurs in respiratory depression (decrease in rate and depth of breathing)-secondary to central nervous system depression.

3) Shunt; This is said to occur when de-saturated blood effectively bypasses oxygenation at the alveolar-capillary level. This can occur a) outside the lungs as in defective development of heart where there is transfer of blood from right heart to left heart without its entry in pulmonary circulation; or b) shunting inside the lungs, that is most commonly due to perfused alveoli. This can occur if the alveoli are atelactatic or if they are filled with the fluid as in pulmonary edema (Both cardiogenic and non-cardiogenic) or with extensive intra alveolar exudation of fluid due to pneumonia.

Cardiogenic pulmonary edema refers to the conditions in which passive diffusion of fluid occurs in alveoli from pulmonary capillary blood due to increase in pulmonary venous pressure as a result of failure of pumping function of heart.

Noncardiogenic pulmonary edema occurs in Adult Respiratory Distress Syndrome (ARDS) distinct from cardiogenic pulmonary edema because in latter pulmonary capillary pressure is elevated where as in ARDS pulmonary capillary pressure is normal. Since the hydrostatic pressures are not elevated there is increased permeability of the alveoli-capillary membranes that occurs via direct chemical injury because of inhaled toxic gases or aspirated acid or indirectly through activation and aggregation of formed elements of blood within pulmonary capillaries in the case of septicemia and/ or endotoxemia. Monocyclic or neutrophilic leucocytes adher to the endothelial surfaces and undergo a respiratory burst to inflict oxidant injury to lung tissue and release mediators of inflammation such as leukotrienes, thromboxanes, prostaglandins, and a series of degeradative enzymes and peptides that directly damage endothelial and alveolar surfaces. This causes leakage of liquid, macromolecules and cellular components from blood to alveoli. This causes mechanical interference in gas exchange between alveolar air and capillary blood. Due to the presence of fluids, surfactant activity is lost and that results into collapse of alveoli and contributes to ventilation perfusion mismatch (VP mismatch).

4) Ventilation perfusion mismatch forms the most common mechanism for hypoxemia in majority of clinical situations. V.P. mismatch can occur in two ways (a) poor perfussion of blood in well ventilated alveoli (b) poor ventilation of air in well purfused alveoli.

The airway diseases like asthma, bronchitis and paranchymal disease like pneumonia, ARDS causes VP mismatch as mechanism of development of hypoxemia.

B] Carbon dioxide (CO_2).is expressed as PCO_2 (partial pressure of CO_2) for practical purpose. Abnormalities of $PaCO_2$ (PCO_2 in arterial blood) termed as *hypercapnea* (increase in $PaCO_2$) and *hypocapnea* (decrease in $PaCO_2$). The essential mechanism underlying all cases of *hypercapnea* is inadequate alveolar ventilation for the amount of CO_2 produced. The contributing factors for *hypercapnea* are

1) Increased CO_2 production (e.g. Hypermetabolic state)

2) Decreased ventilatory drive (as in CNS depression)

3) Respiratory paralysis due to neuromuscular paralysis

4) Inefficiency of gas exchange secondary to VP mismatch

Hypocapnea (decreased $PaCO_2$) results from hyperventilation occuring due to increased rate and / or depth of breathing- a condition called as Carbon-dioxide washout.

ACID-BASE BALANCE

Acid-base balance system is quite active in critically ill patients. Information regarding acid-base biochemistry gives very important information regarding metabolic, renal or kidney disorder and the level of their abnormal function.

Acids are produced continuously during normal metabolism, and the free hydrogen ion (protons) concentration of extra-cellular fluid is fixed within a narrow range. The pH of Extra Cellular Fluid is normally between 7.35 and

7.45. Protons (H^+) are so reactive that even minute change in its concentration influence enzymatic reactions and physiologic processes. Regulation of pH ultimately depends on lungs and kidneys. Lungs excrete acid in form of CO_2 (comes from carbonic acid-H_2CO_3) and hence change in respiration is immediately manifested in change in pH. Kidneys excrete acid in form of H^+ ion but at slower but sustained rate than lungs and compensates for change in pH.

Classification of acid-base disorder is based on measurement of bicarbonate-carbonic acid system, the principal buffer of extra cellular fluid. Because the intra cellular and extra cellular buffers are functionally linked, measurement of plasma bicarbonate system provides useful information about total body buffers. The term Acidosis is defined as a disturbance, which tends to add acid or remove alkali from body fluids, while Alkalosis is any disturbance which tends to remove acid. Metabolic disorders are those in which the primary disturbance is in concentration of bicarbonate. According to Henderson-Hansenbalch equation (Norman, 1991) increased HCO_3 concentration causes increased pH (alkalosis) and decreased HCO_3 concentration causes decreased pH (acidosis). Respiratory disorders are those in which the primary changes is in the concentration of carbon-dioxide (carbonic acid). According to Henderson-Hansenbalch equation, a fall in CO_2 concentration in blood causes alkalemia while rise in CO_2 concentration causes acidemia (acidosis).

A major problem in assessment of acid-base disorder results from the compensatory responses of the lungs and kidneys. A primary change in carbon-dioxide concentration (respiratory pathology) induces a compensatory renal response, which alters plasma bicarbonate in the same direction (renal compensation). Conversely, a primary alteration in plasma bicarbonate (metabolic disorder) induces a compensation in respiratory response, which

changes plasma carbon dioxide in the same direction (respiratory compensation).

TYPES OF ACID-BASE ABNORMALITIES

1. Metabolic acidosis: It is caused by one of the three mechanisms

a) Increased production of non volatile acids as occurs in anaerobic metabolism that produces lactic acid causing lactic acidosis. This is seen in tissue hypoxia due to less oxygen in blood or poor blood perfusion in tissues. This is most commonly encountered acidosis in clinical practice.

b) Decreased acid excretion by kidneys as occurs in kidney failure due to diseases like Malaria, Glomerulonephritis, Septicemia etc.

c) Loss of alkali as occurs in sever watery diarrhoea which loses lot of bicarbonate (alkali) rich intestinal juice in stool.

2. Metabolic alkalosis: It is usually initiated by increased loss of acid from stomach and kidney as occurs in excessive vomiting or diuretic therapy, Gastric drainage etc.

3. Respiratory acidosis: Occurs when lung fails in its ventilatory function thereby retains CO_2 in blood, which is in H_2CO_3 form and thus causes acidosis. Common causes include depression of the respiratory center by cerebral disease or drugs, neuro-muscular disorders, cardiopulmonary arrest.

4. Respiratory alkalosis: That occurs due to increased washout of CO_2 in lungs due to hyperventilation. Most commonly seen in Hypoxic state where it compensates for metabolic acidosis due to low oxygen.

These acid-base disorders can exist in individuals form or in various combinations depending upon the basic disease process (Weinberger and Drazen, 1991).

SERUM ELECTROLYTES IN CRITICAL ILLNESS

Circulatory abnormalities occuring in critical illness changes the composition of body fluids significantly which ultimately affects cell function.

1) SODIUM AND WATER:

Combined sodium and water deficits are far more common than isolated deficits of either constituents. Wide varieties of diseases affect the various organs regulating serum sodium levels. Hyponateremia (low serum sodium) or Hypernateremia (high serum sodium) may be a common occurance in critically ill. Its measurement gives an idea for further treatment and helps in diagnosis of clinical situation (Norman 1991).

2) POTASSIUM:

Potassium principally an intracellular cation it is a major determinant of volume of the cell and osmolality of the body fluids. Apart from various functions of potassium in the cell metabolism, in critically ill it is very important for heart as its abnormal blood levels can lead to lethal cardiac arrhythmias (Norman 1991).

Also the Sodium comes out of the cell during the stage of acidosis. Kidney failure also rises serum potassium.

3) BICARBONATE:

Its importance in critical illness is discussed in Acid-base disorder.

Thus in critical illness like MSOF serum electrolyte abnormalities is a common occurrence and their measurement gives helpful information for diagnosis and treatment of the illness.

AIM AND SCOPE OF THE STUDY

The present study was carried out in two different hospitals-Shri Sayaji General Hospital (SSGH) and Bhailal Amin General Hospital (BAGH), in three different groups of patients 1) Those undergoing major surgery 2) Those with multiple fractures and 3) Those having multiple organ system failures (MOSF) The objectives of the study were as follows:

1. To study the effect of stress in acute critical illness on metabolism especially of proteins and sugar.
2. To demonstrate the serial fall in serum levels of plasma proteins like albumin and transferrin, and to compare the magnitude and pattern of serial fall among these proteins in three different groups in two different hospitals.
3. To observe the relation between plasma glucose and insulin in critical illness.
4. To study the important biochemical parameters like arterial blood gases, serum electrolytes (sodium, potassium, bicarbonate), serum creatinine, blood urea in patients with MOSF in BAGH.
5. To study the effect of biochemical changes on course and prognosis of the illness.

6. To evaluate the status of serum albumin and transferrin as a nutritional indicator.

Further scope of the present study is 1) to follow the serum protein changes for longer period than what is done in our study, especially correlating it with nutritional support 2) to study the plasma levels of amino acid like analine, free fatty acids to know protein energy metabolism in critical illness 3) to study different stress hormones changes and their inter-relationships in critical illness and 4) to study the serial biochemical parameters in details among MOSF with similar type of diseases.